THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Ramacciotti E, Barile Agati L, Calderaro D, et al. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. *Lancet* 2021; published online Dec 15. https://doi.org/10.1016/S0140-6736(21)02004-3.

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Ramacciotti E et al**. Rivaroxaban for Thromboprophylaxis after Hospitalization for COVID-19.**

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Executive Committee

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Enrolling centers and site investigators

Enrolling Center	Investigators	Type of center	Number of beds	Dedicated COVID-19 bed during pandemic
Hospital e Maternidade Christóvão da Gama, Santo André, São Paulo:	Eduardo Ramacciotti (PI), Caroline Candida Carvalho de Oliveira, Tânia Benevenuto Caltabiano	Private institution	290	80
Hospital Leforte Liberdade, São Paulo, São Paulo	Valeria Cristina Resende Aguiar (PI), Marcello da Silva Jardim Ribeiro, Igor Marinho	Private institution	350	120
Hospital Leforte Morumbi, São Paulo, São Paulo	Ivan Silva Marinho (PI), Liane Mara Melo Batista	Private institution	150	50
Hospital das Clínicas de Ribeirão Preto HCRPFM-USP, Ribeirão Preto, São Paulo	Edwaldo Edner Joviliano (PI), Milton Sérgio Bohatch Júnior	Public Institution, University Hospital	1200	180
Hospital do Rocio, Campo Largo, Paraná	Cesar de Oliveira Lopes Dusilek (PI), Kengi Itinose, Lucas Rivabem, Carlos Alberto Kenji Nakashima	Private, but public (SUS patients)	1000	320
Hospital Instituto Couto Maia, Salvador, Bahia	Ana Carla Gois Franco (PI), Suzanna Maria Viana Sanches, Karine Almeida Araújo Ramos	Public	500	120
Hospital Pérola Byington, São Paulo, São Paulo	Andre Luiz Malavasi Longo de Oliveira (PI), Renata Fernanda de Oliveira Pereira	Public	148	40
Instituto do Coração – Hospital das Clínicas HCFMUSP, São Paulo, São Paulo	Daniela Calderaro (PI), Marcus Vinicius Barbosa Santos	Public Institution, University Hospital	2400	795
Hospital das Clínicas de Botucatu – Unesp, Botucatu, São Paulo	Marcone Lima Sobreira (PI)	Public Institution, University Hospital	550	80
HAPVIDA, Fortaleza, Ceará:	Bruno Bezerra de Menezes Cavalcante (PI	Private	700	150
Hospital Municipal de Barueri Dr. Francisco Moran, Barueri, São Paulo	Paulo Fernando Guimarães Morando Marzocchi Tierno (PI), Nara Franzin de Moraes	Public	289	192
Hospital Nossa Senhora das Graças, Curitiba, Paraná	Ricardo Cesar Rocha Moreira (PI), Giana Caroline Strack Neves, Izara de Castro e Souza, Bruno Moraes Ribas, Flavia Ramos Tristão.	Public (75%) and Private	750	150
Irmandade de misericordia da Santa Casa de Santos, Santos, SP	Rogério Dedivits and André Sementilli	Public	920	300
Hospital Erasto Gaertner, Curitiba, Paraná	Fabiano Erzinger	Public	153	30

Outcomes Definitions

Primary Outcome

The primary outcome will be a composite of symptomatic VTE, VTE-related death, and VTE detected at mandatory bilateral lower limbs venous duplex scan and computed tomography pulmonary angiogram and symptomatic ATE (myocardial infarction (MI), non-hemorrhagic stroke, major adverse limb event (MALE), and cardiovascular (CV) death at day 35 analyzed in the ITT population.

Secondary Outcomes

Secondary Efficacy Outcomes

Secondary endpoints are to compare rivaroxaban with standard post-hospital discharge treatment in clinically ill patients at high risk for VTE:

- VTE-related death (death by PE or death in which PE cannot be excluded as the cause) and symptomatic VTE (DVT of the lower extremities and non-fatal PE).
- The composition of symptomatic VTE (DVT of the lower extremities and non-fatal PE) and all-cause mortality.
- The composition of symptomatic VTE (DVT of the lower extremities and non-fatal PE), myocardial infarction (IM), non-hemorrhagic stroke and cardiovascular death (CV) (death from known CV and death in which the CV cause cannot be excluded; by this definition, a VTE-related death is considered a CV death).

Primary Safety Outcome

The primary safety endpoint is major bleeding as defined by the International Society of Thrombosis and Haemostasis (ISTH) criteria:

- A major bleeding event according to ISTH is defined as evident hemorrhage associated with decrease in hemoglobin levels of 2 g/dl or higher or leading to transfusion of two or more units of red blood concentrate or whole blood, or hemorrhage occurring in a critical site: e.g., intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartmental, retroperitoneal syndrome, or a fatal outcome.

Secondary Safety Outcomes

The secondary safety outcomes will be a combination of major bleeding, clinically relevant nom major bleeding and all bleeding, also defined by the ISTH criteria:

- Clinically relevant non-significant bleeding is defined as an evident hemorrhage not meeting the criteria of significant bleeding but associated with medical intervention, unscheduled contact (visit or phone call) with a doctor, interruption (temporary) of study treatment, or associated with discomfort to the participant such as pain or impairment of daily activities.
- Another bleeding is defined as any other evident hemorrhage that does not meet the ISTH criteria for significant or non-significant clinically relevant hemorrhage.

Table S1. Eligibility criteria for MICHELLE trial

Inclusion criteria
1. Male and nonpregnant female patients 18 years of age or older.
2. Positive reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay for SARS-CoV-2 in a respiratory tract sample.
3. Pneumonia confirmed by chest imaging.
4. ≥ 3 days of hospitalization
5. Both groups should have received prophylactic doses of enoxaparin (40 mg SC once daily), fondaparinux (2.5 mg once daily), or unfractionated heparin (UFH, 5.000 IU twice or three times a day), during the hospital stay.
6. Additional risk factors for VTE, as indicated by a total modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) risk score of 4 or higher (scores range from 0 to 10, with higher scores indicating a higher risk of venous thromboembolism) or a risk score of 2 or 3 plus a plasma d-dimer level of more than twice the upper limit of the normal range at the time of discharge.
7. Agreement to participate by providing the informed consent form
Exclusion Criteria
1. Age <18 years.
2. Physician decision that involvement in the trial was not in the patient's best interest.
3. Any hemorrhage (defined as hemorrhage requiring hospitalization, transfusion, surgical intervention, invasive procedures, occurring in an anatomically critical site, or causing disability) within three months before randomization or occurring during the initial hospitalization period.
4. Major surgery, parenchymal organ biopsy, ophthalmic surgery (excluding cataract surgery) or serious trauma (including head trauma) within four weeks prior to randomization. The investigator's criterion should be applied, but the following guidelines can be considered for the purpose of this study: Major surgeries often involve opening one or more major body cavities: the abdomen, chest, or skull, and can stress vital organs. Major surgeries are usually performed using general anesthesia in a hospital operating room by a surgeon (or surgeons) and usually require admission for at least one night in the hospital after surgery. On the other hand, with minor surgeries, the main body cavities are not opened. Minor surgeries may involve the use of local, regional, or general anesthesia and can be performed in the emergency room, in an outpatient operating room, or in a clinical office. Vital organs are usually not stressed, and surgery can be performed by a single doctor, who may or may not be a surgeon. In general, the person can return home on the same day that minor surgery is performed. The investigator's criteria should be applied, but fracture or concussion should be considered serious head trauma, although external trauma without fracture or concussion may be considered for inclusion.
5. Any major planned surgery (see exclusion criterion #2) or important invasive diagnostic procedure provided for during the clinical study.
6. Participants with any known coagulopathy or hemorrhagic diathesis or an international normalized ratio (INR) > 1.5 during initial hospitalization without a subsequent value (the last value before randomization) that is ≤ 1.5.
7. A history of hemorrhagic stroke or any intracranial hemorrhage at any time in the past, evidence of primary intracranial hemorrhage on CT or MRI imaging of the brain, or clinical presentation consistent with intracranial hemorrhage. This also applies to participants hospitalized due to ischemic stroke at randomization. Participants with hemorrhagic transformation of an ischemic infarction prior to randomization are not excluded unless there is evidence of parenchyma hemorrhage (types HP-1 and HP-2): Hemorrhagic infarction type 1 (IH-1) is defined as a small petechiae along the margins of the infarction and type 2 IH (IH-2) is defined as more confluent petechiae within the infarcted area, but without expansive effect. HP type 1 (HP-1) is defined as hematoma in ≤ 30% of the infarct area with some mild expansive effect; HP type 2 (HP-2) is defined as dense hematoma > 30% of the infarction area with substantial expansive effect or as any hemorrhagic lesion outside the infarction area (Berger, 20012). Participants with type 1 and IH-2 hemorrhagic infarction are NOT excluded from this study, but participants with HP-1 and HP-2 are excluded from this study.
8. The participant has a history or presence of intracranial neoplasia (benign or malignant), brain metastases, arteriovenous malformation (VA) or aneurysm
9. Active gastroduodenal ulcer, defined as diagnosed at three months, or current known or symptomatic arteriovenous malformations of the gastrointestinal tract.
10. Platelet count in the screening < 50 x 109 cells/l.

11. Active cancer (excluding non-melanoma skin cancer), defined as cancer that is not in remission or requires active chemotherapy or auxiliary therapies such as immunotherapy or radiotherapy. Chronic hormone therapy (e.g., tamoxifen, anastrozole, leuprolide acetate) is allowed for cancer in remission.
12. Any clinical picture (e.g., atrial fibrillation) requiring the use of any parenteral(s) or oral anticoagulant(s) (e.g., sodic warfarin or vitamin K antagonists, factor II inhibitors or Xa, fibrinolytics) concomitantly with the study drug.
13. Bilateral and unilateral amputation of the lower extremities above the knee.
14. Participant presenting allergy, hyper or known intolerance to rivaroxaban or any of its excipients.
15. Severe renal failure (baseline CrCl < 30 ml/min calculated using the Cockcroft-Gault)
16. Known significant liver disease (e.g., acute hepatitis, active chronic hepatitis, cirrhosis) that is associated with coagulopathy or moderate or severe hepatic impairment.
17. Known HIV infection.

Table S2. Suggested prophylactic scheme during hospitalization

CrCl	BMI	Enoxaparin	Fondaparinux	UFH
≥30	<40	40 mg SC every 24h	2·5 mg SC daily	5,000 units SC every 8 to 12 hours
	≥40	60 mg SC every 24h or 40 mg SC every 12 hours	Not recommended	7,500 units SC every 8 to 12 hours
<30	<40	UFH 5,000 units SC every 8 to 12 hours		
	≥40	UFH 7,500 units SC every 8 to 12 hours		

BMI indicates body mass index; CrCl, creatinine clearance; SC, subcutaneous; UFH, unfractionated heparin.

Table S3. Compliance with the study protocol

	Period of treatment arm migration		
Treatment Arm	**≤ 48 hours**	**≥48 hours ≤ 7 days**	**> 7 days**
Rivaroxaban*	0	1 (0.62%)	2 (1.25%)
Control†	0	1 (0.62%)	7 (4.37%)

*Treatment deviation: Rivaroxaban to anticoagulants
Three patients (ID 46, 141 and 147) randomized to the rivaroxaban arm had their treatment discontinued at some point from discharge to day 35. Two of them were motivated by an allergic reaction to rivaroxaban.
†Treatment deviation: no anticoagulation
Eight patients (ID 15, 23, 37, 86, 171, 186, 206 and 262) randomized to the placebo arm received direct oral anticoagulant at some point from discharge to day 35.
We considered for per-protocol analysis
≤ 48 hours = no deviation
≥48 hours ≤ 7 days = temporary deviation
> 7 days = definitive deviation

For per-protocol analysis, patients with definitive deviations were excluded.

Table S4. Sensitivity analysis using per-protocol population

	Rivaroxaban (N = 155)	**Control (N = 152)**	**Relative Risk (95% CI)**
Primary efficacy outcomes	4/155 (2.58%)	15/152 (9.87%)	0.26 (0.09 – 0.77)
Secondary efficacy outcomes			
Symptomatic + fatal venous thromboembolism	1/155 (0.65%)	8/152 (5.26%)	0.12 (0.02 – 0.97)
Symptomatic venous thromboembolism and all-cause mortality	4/155 (2.58%)	9/152 (5.92%)	0.44 (0.14 – 1.39)
A composite of Symptomatic venous thromboembolism, myocardial infarction, stroke, and cardiovascular deaths	1/155 (0.65%)	9/152 (5.92%)	0.11 (0.01 – 0.85)
Components of the primary outcome			
Symptomatic DVT	0	3/152 (1.97%)	0.14 (0.01 – 2.69)
Symptomatic PE	1/155 (0.65%)	2/152 (1.32%)	0.49 (0.04 – 5.35)
Fatal PE	0	3/152 (1.97%)	0.14 (0.01 – 2.69)
Asymptomatic DVT detected at duplex scan	2/155 (1.29%)	1/152 (0.66%)	1.96 (0.18 – 21.40)
Asymptomatic PE detected at CT pulmonary angiogram	1/155 (0.65%)	4/152 (2.63%)	0.25 (0.03 – 2.17)
Symptomatic arterial thrombosis	0	1/152 (0.66%)	0.33 (0.01 – 7.96)
Myocardial infarction	0	0	-
Non-haemorrhagic stroke	0	0	-
Major adverse limb event (MALE)	0	0	-
Cardiovascular deaths	0	1/152 (0.66%)	0.33 (0.01 – 7.96)
Primary safety outcomes			
Major bleeding	0	0	-
Secondary safety outcomes			
Clinically relevant nonmajor bleeding	2/155 (1.29%)	2/152 (1.32%)	0.98 (0.14 – 6.87)
Other bleeding	2/155 (1.29%)	1/152 (0.66%)	1.96 (0.18 – 21.40)
A combination of major and clinically relevant non-major bleeding and other bleeding	4/155 (2.58%)	3/152 (1.97%)	1.31 (0.30 – 5.74)

Per-protocol analysis. On the rivaroxaban group, 5 patients were excluded from the analysis: 2 did not receive the intervention (1 allocated to another study, 1 prolonged hospitalization), 2 did not reach the

compliance for anticoagulation use (≥7 days of discontinuation) and 1 withdrew the informed consent. One of the discontinued patients had a primary outcome event (asymptomatic venous thromboembolism). This patient was discontinued due to urticaria. On the control group, 8 patients were excluded for the per-protocol analysis: 1 informed consent withdrawal, and 7 for protocol violation (we considered discontinuation on the control group if the patient received ≥ 7 days of any anticoagulant therapy).

Table S5. Efficacy and safety outcomes using Wilson CI

Outcomes	Rivaroxaban (N=159)	Control (N=159)	Risk Difference (95% Wilson CI)
Primary efficacy outcome, no./No. (%)	5/159 (3·14%)	15/159 (9·43%)	-0·06 (-0·12; -0.01)
Secondary efficacy outcomes, no./No. (%)			
Symptomatic and fatal VTE	1/159 (0·63%)	8/159 (5·03%)	-0·04 (-0·09; -0·01)
Symptomatic VTE and all-cause mortality	4/159 (2·52%)	9/159 (5·66%)	-0·03 (-0·08; 0·01)
Composite of symptomatic VTE, MI, stroke, and cardiovascular death	1/159 (0·63%)	9/159 (5·66%)	-0·05 (-0·10; -0·01)
Components of the primary outcome, no. (%)			
Symptomatic DVT	0	3 (1·89%)	-0·02 (-0·05; 0·01)
Symptomatic PE	1 (0·63%)	2 (1·26%)	-0·01 (-0·04; 0·02)
Fatal PE	0	3 (1·89%)	-0·02 (-0·05; 0·01)
Asymptomatic DVT on duplex scan	3 (1·89%)	1 (0·63%)	0·01 (-0·02; 0·05)
Asymptomatic PE on CT pulmonary angiogram	1 (0·63%)	4 (2·52%)	-0·02 (-0·06; 0·01)
Symptomatic arterial thrombosis	0	1 (0·63%)	-0·01 (-0·03; 0·02)
MI	0	0	0·00 (-0·02; 0·02)
Non-haemorrhagic stroke	0	0	0·00 (-0·02; 0·02)
Major adverse limb event	0	0	0·00 (-0·02; 0·02)
Cardiovascular death	0	1 (0·63%)	-0·01 (-0·03; 0·02)
Primary safety outcome, no. (%)			
Major bleeding	0	0	0·00 (-0·02; 0·02)
Secondary safety outcomes, no. (%)			
CRNM	2/159 (1·26%)	2/159 (1·26%)	0·00 (-0·03; 0·03)
Other bleeding	2/159 (1·26%)	1/159 (0·63%)	0·01 (-0·02; 0·04)
Combination of major, CRNM, and other bleeding	4/159 (2·51%)	3/159 (1·89%)	0·01 (-0·03; 0·05)

CI indicates confidence interval; CRNM, clinically relevant nonmajor; CT, computed tomography; DVT, deep vein thrombosis; MI, myocardial infarction; PE, pulmonary embolism; VTE, venous thromboembolism.

Table S6. Sensitivity analysis using Risk Difference with 95% Wilson CI - Per-protocol analysis

	Rivaroxaban (N = 155)	**Control (N = 152)**	**Risk Difference (95% Wilson CI)**
Primary efficacy outcomes	4/155 (2.58%)	15/152 (9.87%)	-0.07 (-0.13; - 0.02)
Secondary efficacy outcomes			
Symptomatic + fatal venous thromboembolism	1/155 (0.65%)	8/152 (5.26%)	-0.05 (-0.09; -0.01)
Symptomatic venous thromboembolism and all-cause mortality	4/155 (2.58%)	9/152 (5.92%)	-0.03 (-0.09; 0.01)
A composite of Symptomatic venous thromboembolism, myocardial infarction, stroke, and cardiovascular deaths	1/155 (0.65%)	9/152 (5.92%)	-0.05 (-0.10; -0.01)
Components of the primary outcome			
Symptomatic DVT	0	3/152 (1.97%)	-0.02 (-0.06; 0.01)
Symptomatic PE	1/155 (0.65%)	2/152 (1.32%)	-0.01 (-0.04; 0.02)
Fatal PE	0	3/152 (1.97%)	-0.02 (-0.06; 0.01)
Asymptomatic DVT detected at duplex scan	2/155 (1.29%)	1/152 (0.66%)	0.01 (-0.02; 0.04)
Asymptomatic PE detected at CT pulmonary angiogram	1/155 (0.65%)	4/152 (2.63%)	-0.02 (-0.06; 0.01)
Symptomatic arterial thrombosis	0	1/152 (0.66%)	-0.01 (-0.04; 0.02)
Myocardial infarction	0	0	0.00 (-0.02; 0.02)
Non-haemorrhagic stroke	0	0	0.00 (-0.02; 0.02)
Major adverse limb event (MALE)	0	0	0.00 (-0.02; 0.02)
Cardiovascular deaths	0	1/152 (0.66%)	-0.01 (-0.04; 0.02)
Primary safety outcomes			
Major bleeding	0	0	0.00 (-0.02; 0.02)
Secondary safety outcomes			
Clinically relevant nonmajor bleeding	2/155 (1.29%)	2/152 (1.32%)	0.00 (-0.04; 0.03)
Other bleeding	2/155 (1.29%)	1/152 (0.66%)	0.01 (-0.02; 0.04)
A combination of major and clinically relevant non-major bleeding and other bleeding	4/155 (2.58%)	3/152 (1.97%)	0.01 (-0.03; 0.05)

Per-protocol analysis. On the rivaroxaban group, 5 patients were excluded from the analysis: 2 did not receive the intervention (1 allocated to another study, 1 prolonged hospitalization), 2 did not reach the compliance for anticoagulation use (≥7 days of discontinuation) and 1 withdrew the informed consent.

One of the discontinued patients had a primary outcome event (asymptomatic venous thromboembolism). This patient was discontinued due to urticaria. On the control group, 8 patients were excluded for the per-protocol analysis: 1 informed consent withdrawal, and 7 for protocol violation (we considered discontinuation on the control group if the patient received ≥ 7 days of any anticoagulant therapy).

Table S7. Detailed safety outcomes in the safety population

Variables	Treatment	Control	Relative Risk	P-Value
	n = 159	n = 159		
ISTH Major bleeding	0 (%)	0 (%)	---	---
Decrease in haemoglobin ≥ 2g/dl	0 (%)	0 (%)	---	---
Need for transfusion	0 (%)	0 (%)	---	---
Critical bleeding*	0 (%)	0 (%)	---	---
Fatal bleeding	0 (%)	0 (%)	---	---
	---		---	
Clinically relevant non-major bleeding	2/159 (1·26%)	2/159 (1·26%)	1·00 (0·14–7·01)	1·0000
Other bleeding	2/159 (1·26%)	1/159 (0·63%)	2·00 (0·18–21·84)	0·5698
Combination of major, CRNM, and other bleeding	4/159 (2·51%)	3/159 (1·89%)	1·33 (0·30–5·86)	0·7034

* Critical bleeding was defined as if they occurred in intracranial, intraspinal, pericardial, intraarticular, intramuscular, or retroperitoneal sites

Table S8. Subgroup analysis using Wilson CI

SUBGROUP		Rivaroxaban no./No. (%)	Control no./No. (%)	Risk Difference (95% Wilson CI)
Age (yrs.)	≤60	2/77 (2·60%)	4/92 (4·35%)	-0·02 (-0·08; 0·05)
	>60	3/82 (3·66%)	11/67 (16·42%)	-0·13 (-0·24; -0·03)
BMI	≤30	3/105 (2·86%)	10/88 (11·36%)	-0·09 (-0·17; - 0·01)
	>30	2/54 (3·70%)	5/71 (7·04%)	-0·03 (-0·12; 0·06)
Creatinine Clearance ml/min	30 to <50 ml/min	0/6	0/5	0·00 (-0·43; 0·39)
	≥50 ml/min	5/152 (3·29%)	15/154 (9·74%)	-0·06 (-0·12; -0·01)
Modified IMPROVE VTE risk score	2-3	2/98 (2·04%)	9/99 (9·09%)	-0·07 (-0·14; -0·004)
	≥4	3/61 (4·92%)	6/60 (10·0%)	-0·05 (-0·16; 0·05)
D-Dimer level above the UNL	≤500 ng/ml	0/9 (0·00%)	1/10 (10·00%)	-0·10 (-0·40; 0·21)
	>500 ng/ml	4/106 (3·77%)	10/108 (9·26%)	-0·05 (-0·13; 0·01)
Antiplatelets use — no. (%)	no	5/151 (3·31%)	14/151 (9·27%)	-0·07 (-0·12; -0·004)
	yes	0/8 (0·00%)	1/8 (12·5%)	-0·13 (-0·47; 0·22)

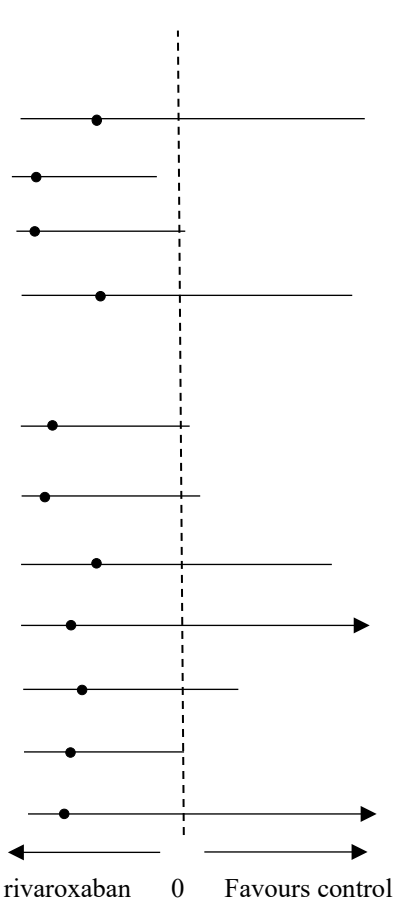


Table S9. DELTA2 checklist

Recommended reporting items	**Page and line numbers where item is reported**
Primary outcome (and any other outcome on which the calculation is based)	Reported on page 9, lines 10-13 on the main manuscript and on supplementary material, page 4
If a primary outcome is not used as the basis for the sample size calculation, state why	NA
(2) Statistical significance level and power	Reported on page 10, lines 20-22, main manuscript
(3) Express the target difference according to outcome type	Reported on page 10, line 23, main manuscript
(a) Binary—state the target difference as an absolute or relative effect (or both), along with the intervention and control group proportions. If both an absolute and a relative difference are provided, clarify if either takes primacy in terms of the sample size calculation	Reported on page 10, line 23, main manuscript
(b) Continuous—state the target mean difference on the natural scale, common standard deviation, and standardised effect size (mean difference divided by the standard deviation)	NA
(c) Time-to-event—state the target difference as an absolute or relative difference (or both); provide the control group event proportion, planned length of follow-up, intervention and control group survival distributions, and accrual time (if assumptions regarding them are made). If both an absolute and relative difference are provided for a particular time point, clarify if either takes primacy in terms of the sample size calculation	Time to event was not used. NA
(4) Allocation ratio	Page 11, line 1
If an unequal ratio is used, the reason for this should be stated	NA
(5) Sample size based on the assumptions as per above	Page 10, line 21
(a) Reference the formula/sample size calculation approach, if standard binary, continuous, or survival outcome formulas are not used. For a time-to-event outcome, the number of events required should be stated	NA
(b) If any adjustments (eg, allowance for loss to follow-up, multiple testing) that alter the required sample size are incorporated, they should also be specified, referenced, and justified along with the final sample size	NA
(c) For alternative designs, additional input should be stated and justified. For example, for a cluster randomised controlled trial (or an individually randomised controlled trial with clustering), state the average cluster size and intra-cluster correlation coefficient(s). Variability in cluster size should be considered and, if necessary,	NA

the coefficient of variation should be incorporated into the sample size calculation. Justification for the values chosen should be given	
(d) Provide details of any assessment of the sensitivity of the sample size to the inputs used	NA
(7) Explain the choice of target difference—specify and reference any formal method used or relevant previous research	Page 10, line 20-22 and page 15, lines 7-13
Additional item for trial results paper	NA
(8) Reference the trial protocol	Page 7, line 23.

Figure S1. Subgroup sensitivity analysis

SUBGROUP		Rivaroxaban n./total (%)	Control n./total (%)	RR (95% CI)
Age (yrs.)	≤60	2/76 (2.63%)	4/88 (4.55%)	0.58 (0.11 – 3.07)
	>60	2/79 (2.53%)	11/64 (17.19%)	0.15 (0.03 – 0.64)
BMI	≤30	2/102 (1.96%)	10/84(11.90%)	0.16 (0.04 – 0.73)
	>30	2/53 (3.77%)	5/68 (7.35%)	0.51 (0.10 – 2.54)
Creatinine Clearance ml/min	30 to <50 ml/min	0/5	0/4	---
	≥50 ml/min	4/150 (2.67%)	15/148 (10.14%)	0.26 (0.09 – 0.77)
Modified IMPROVE VTE risk score	2-3	2/96 (2.08%)	9/92 (9.78%)	0.21 (0.05 – 0.96)
	≥4	2/59(3.39%)	6/60 (10.0%)	0.34 (0.07 – 1.61)
D-Dimer level above the UNL	≤500 ng/ml	0/9 (0.00%)	1/10 (10.00%)	0.37 (0.02 – 7.99)
	>500 ng/ml	4/104 (3.85%)	10/101 (9.90%)	0.39 (0.13 – 1.20)
Antiplatelets use — no. (%)	no	4/147 (2.72%)	14/144 (9.72%)	0.28 (0.09 - 0.83)
	yes	0/8 (0.00%)	1/8 (12.5%)	0.33 (0.02 – 7.02)

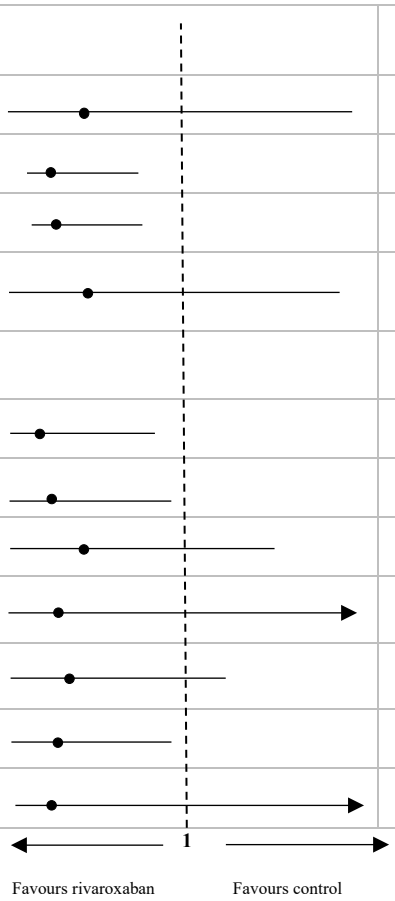


Figure S2. Primary efficacy and safety outcomes (intention-to-treat analysis)

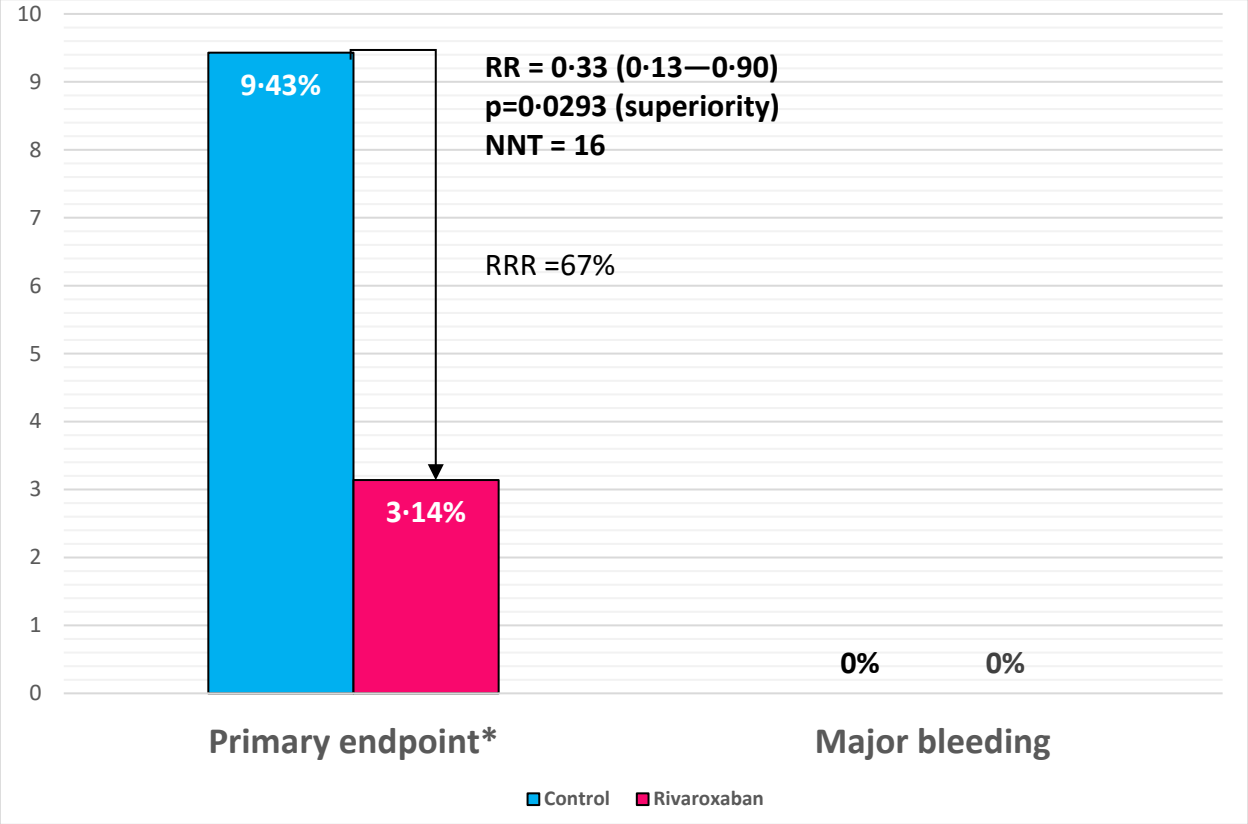
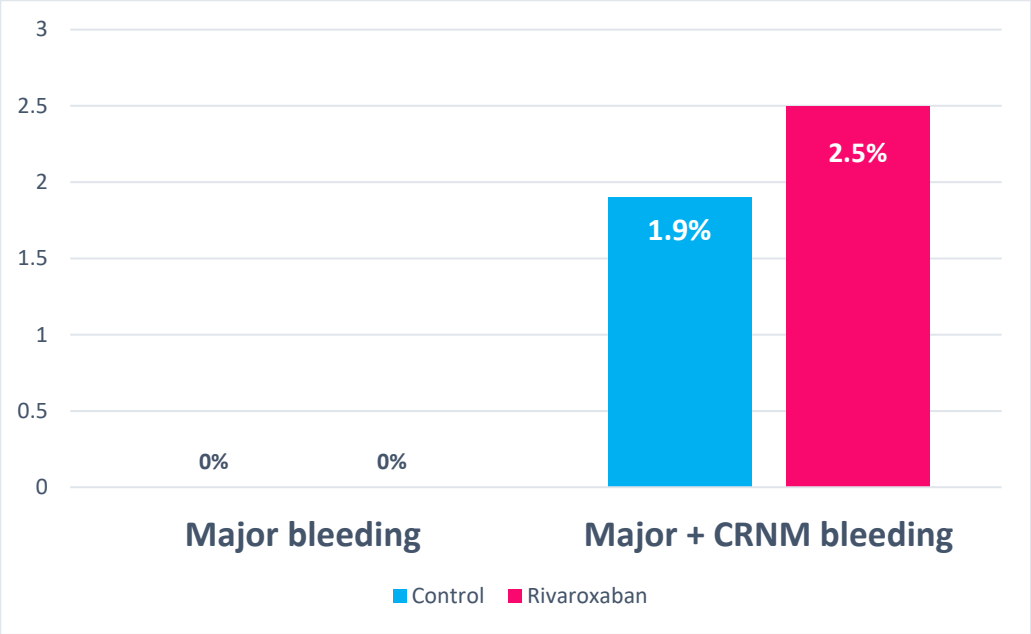


Figure S3. Bleeding endpoints results



Interim analysis

A single interim analysis was carried out in the first 200 patients. The primary efficacy outcome occurred in three of 99 patients (3·03%) assigned to rivaroxaban and 11 of 100 patients (11%) assigned to no anticoagulation (relative risk 0·27; 95% confidence interval [CI] 0·08–0·96; p=0·0426). No major bleeding occurred in either study group.

The interim analysis was performed by an unblinded statistician who discussed the results with the DSMB members only. These results were not shared with the trial leadership or with anyone outside of the DSMB. By the time the 200-patient interim analysis was conducted (including 35 days of follow-up), 287 patients had already been enrolled into the trial and we were very close to the planned final sample size of 320 patients. The initial sample size was calculated assuming a power of 80%, a significance level of 0·05, with a relative risk reduction of around 67%. The interim analysis showed a 73% relative risk reduction for the primary outcome. Although a re-estimation of the sample size was initially considered, based on these findings and on the fact that the study enrolment was very close to completion, the DSMB recommended the trial continue as planned and there was no need to re-estimate the sample size.

Protocol Summary of Changes

Reference: Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised controlled trial

The original version of the protocol was 1.0 and was dated July 14, 2020.
The final version of the protocol was 2.0 and was dated April 1, 2021.
The amendments to the protocol, their rationale and summary of changes are presented below:

Amendment to the Protocol – Version 2.0 (April 1, 2021)

Amendment Rationale

- **Update of objective and primary efficacy results including arterial events in the composition of the primary outcome:**
  The main objective is to evaluate the efficacy and safety of rivaroxaban compared to standard treatment in the prevention of symptomatic venous thromboembolism (VTE: deep vein thrombosis [DVT] of the lower extremities and non-fatal pulmonary embolism [PE]) and VTE-related death (death by and or death in which A cannot be excluded as the cause) in combination with asymptomatic VTE (detected by doppler ultrasound of the lower limbs and pulmonary angiotomography performed after hospital discharge), in addition to acute myocardial infarction, non-hemorrhagic stroke, major adverse limb event (arterial ischemia) or cardiovascular death in patients clinically ill with COVID-19 discharged from the hospital at high risk for VTE.

Changes to the protocol

- **Synopsis of the protocol:**
  - General objectives and Primary efficacy outcomes sections were included: Objective was re-writing and re-organized for greater clarity based on the changes of primary outcome.

  - Secondary efficacy outcomes: Correction and wording changing for Primary objectives.

  - Safety outcomes and Secondary safety outcomes: Re-organization of the Security Objectives.

  - Hypothesis: The Hypothesis was re-writing based on the changes of primary outcome. Secondary hypothesis was excluded.

  - Overview: The Overview was re-writing based on the changes of primary outcome.

  - Evaluations / Efficacy Results: The Evaluations / Efficacy Results was re-writing based on the changes of primary outcome.

  - Statistical Methods: The procedures for sample size calculation were re-writing for greater clarity and the relative risk reduction (RRR) updated (66.67%).

- Primary efficacy result: Primary efficacy analysis will be based on the ITT analysis which was re-written to clarify the relative risk measures. The description of the primary efficacy analysis based on the time from randomization to the first occurrence of primary efficacy endpoints was excluded.

- Bleeding results: Wording changing - Hemorrhagic results. The safety results will be analyzed by number of bleeding events up to day 35 relative risks and not more by the first occurrence of bleeding events.

- **Section 2.1.3:** The definitions of the outcome events to be analyzed by the Committee of Clinical Events (CEC) were updated: symptomatic VTE, VTE-related death, asymptomatic VTE (Doppler and AngioCT scan) and symptomatic ATE, MI, non-hemorrhagic stroke, (MALE), and cardiovascular death at day 35. The CEC will also evaluate bleeding events.

- **Section 9.1:** The primary efficacy result was updated based on the changes of primary outcome.

- **Section 11:** Time to event analysis procedures were excluded. The procedures for sample size calculation were re-writing for greater clarity and the relative risk reduction (RRR) updated (66.67%).

- **Section 11.3.1:** Analysis of the primary efficacy outcomes were re-writing for greater clarity based on the changes of primary outcome, as well as due to the exclusion of the analysis based on the time from randomization to the first occurrence of primary efficacy endpoints. Only the relative risk reduction (RRR) will be estimated.

- **Section 11.4:** Safety analysis was re-writing and re-organized for greater clarity based on the Primary safety outcomes, Secondary safety outcomes, and Sensitivity Analyses.

Wilson Confidence Interval for a Risk Difference

As with relative risk, a 95% confidence interval for the risk difference can be calculated by score (Wilson).

Suppose we have two populations from which dichotomous (binary) responses will be recorded. The probability (or risk) of obtaining the event of interest in population 1 (the treatment group) is p_1 and in population 2 (the control group) is p_2.

Random samples of n_1 and n_2 subjects are obtained from these two populations. Suppose we have x_1 and x_2 events in population 1 and 2, respectively. The assumption is made that the events x_1 and x_2 from each group follow a binomial distribution with the event probability p_i (I =1, 2) and sample size n_i (i=1, 2), respectively. This means that the event probability p_i (i= 1, 2) is the same for all subjects within a population and that the response from one subject to the next is independent of one another. Now we can define the observed proportion of events for these groups as $\hat{p_1} = x_1/n_1$ and $\hat{p_2} = x_2/n_2$, respectively. Let z correspond to the α/2- percentile of the normal distribution. As an example, for a 95%CI (γ = 0.95 or α=0.05), the corresponding z value would approximately be 1.96.

The lower and upper Wilson (Score) confidence limits without continuity correction for p_i (i = 1, 2) are given by:

$$L_i(p_i) = L_i = \frac{1}{2(n_i+z^2)}\left((2n_i\hat{p}_i + z^2) - z\sqrt{4n_i\hat{p}_i(1-\hat{p}_i)+z^2}\right),$$

and

$$U_i(p_i) = U_i = \frac{1}{2(n_i+z^2)}\left((2n_i\hat{p}_i + z^2) + z\sqrt{4n_i\hat{p}_i(1-\hat{p}_i)+z^2}\right).$$

Finally, the lower and upper Wilson confidence limits for Risk Difference ($p_1 - p_2$) are given by:

$$(\hat{p}_1 - \hat{p}_2) - \sqrt{(\hat{p}_1 - L_1)^2 + (U_2 - \hat{p}_2)^2},$$

and

$$(\hat{p}_1 - \hat{p}_2) + \sqrt{(U_1 - \hat{p}_1)^2 + (\hat{p}_2 - L_2)^2}.$$

Reference:
Newcombe R. Interval Estimation for the Difference Between Independent Proportions: Comparison of Eleven Methods. Stat Med 1998;17:873-90.

Garner W. Constructing Confidence Intervals for the Differences of Binomial Proportions in SAS®. Gilead Sciences, Inc., Foster City, CA. Available at: https://lexjansen.com/wuss/2016/127_Final_Paper_PDF.pdf. Accessed October 20, 2021.

Statistical Analysis Plan

Introduction

The devastating Coronavirus disease (COVID-19) pandemic is associated with a high prothrombotic state. It is unclear if the coagulation abnormalities occur because of the direct effect of SARS-CoV-2 or indirectly by the cytokine storm and endothelial damage or by a combination of mechanisms. There is a clear indication of in-hospital pharmacological thromboprophylaxis for every patient with COVID-19 after bleed risk assessment. However, there is much debate regarding the best dosage regimen, and there is no consensus on the role of extended thromboprophylaxis.

Considering the in-hospital venous thromboembolism (VTE) burden of COVID-19 and previous data on medically ill patients showing that more than half of the VTE events occur after hospital discharge,[1] it is reasonable to question the potential role of extended VTE and arterial thromboembolism (ATE) prophylaxis in the post-hospital discharge setting for these patients.

2. Objective

To evaluate the safety and efficacy of rivaroxaban 10 mg once daily for 35±4 days versus no intervention after hospital discharge in COVID-19 patients who were at increased risk for VTE and ATE and have received parenteral VTE prophylaxis during hospitalization.

Study Design

It is a prospective, randomized, multicenter, open-label trial designed to test the efficacy and safety of extended thromboprophylaxis of rivaroxaban for 35±4 days *versus* no pharmacologic intervention after hospital discharge in COVID-19 patients who were at increased risk for VTE and ATE and have received parenteral VTE prophylaxis during hospitalization. Patients will be assigned at hospital discharge to either once daily rivaroxaban at a dose of 10 mg once daily or regular follow-up for 35±4 days, without extended anticoagulation (Figure 1). Both groups should have received prophylactic doses of enoxaparin (40 mg SC c), unfractionated heparin (UFH, 5.000 IU twice or three times a day), or fondaparinux (2.5 mg once daily) during the hospital stay. The study's primary objective is to determine the superiority of rivaroxaban versus no pharmacological intervention after discharge for hospitalization for COVID-19 infection. This is not a placebo-controlled study – the control arm receives no placebo medication. The study design is depicted in Figure 1. The IMPROVED VTE score is described in Table 1.

Visit schedule

Patients will be screened for the eligibility criteria during hospitalization and will be randomized after providing informed consent. Medication will be provided at randomization and must be started within the first 24 hours after hospital discharge and maintained for 35 days, irrespective of the second evaluation day (Figure 2). At randomization, patients will be encouraged to report in the protocol evaluations or by extra-telephone calls any symptom suggestive of VTE or bleeding. In every consultation, the investigators will perform detailed surveillance about chest pain, dyspnea, peripheral edema, pain in the lower limbs, and bleeding signs.

The first evaluation will be on day 7 after randomization and can be either by telephone call or at the outpatient clinic. The second evaluation will be on day 35 ± 4 at the outpatient clinic. On the same day, computed tomography pulmonary angiogram (CTPA) and lower limbs venous Duplex scan will be performed. The third and last protocol evaluation will be on day 75±5, by telephone call or at the outpatient clinic (Figure 2).

Inclusion Criteria

Male and nonpregnant female patients 18 years of age or older.

Agreement to participate by providing the informed consent form (ICF).

Positive reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay for SARS-CoV-2 in a respiratory tract sample.

Pneumonia confirmed by chest imaging.

≥ 3 days of hospitalization

Have received thromboprophylaxis with low-molecular-weight heparin, fondaparinux, or unfractionated heparin during the index hospitalization.

Additional risk factors for VTE, as indicated by a total modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) risk score of 4 or higher (scores range from 0 to 10, with higher scores indicating a higher risk of venous thromboembolism; minimal clinically important difference, 2) or a risk score of 2 or 3 plus a plasma d-dimer level of more than twice the upper limit of the normal range at the time of discharge (Table 1).

Agreement to participate by providing the informed consent form

Exclusion Criteria

Age < 18 years.

Refusal of informed consent.

Physician decision that involvement in the trial was not in the patient's best interest.

Patients with a medical indication for anticoagulation therapy at the time of inclusion (for example, diagnosis of venous thromboembolism, atrial fibrillation, mechanical valve prosthesis).

Platelets < 50,000 / mm^3.

Patients with contraindications to anticoagulation (active bleeding, liver failure, blood dyscrasia, or prohibitive hemorrhagic risk in the investigator's assessment).

Active cancer (excluding non-melanoma skin cancer) defined as cancer, not in remission or requiring active chemotherapy or adjunctive therapies such as immunotherapy or radiotherapy.

Use of strong inhibitors of cytochrome P450 (CYP) 3A4 and/or glycoprotein P (P-gp) (eg, protease inhibitors, ketoconazole, Itraconazole) and/or use of P-gp and strong inducers of CYP3A4 (how but not limiting rifampicin/rifampicin, rifabutin, rifapentine, phenytoin, phenobarbital, carbamazepine or St. John's wort).

Creatinine clearance <30 ml / min.

Pregnancy or breastfeeding.

Known HIV infection.

Presence of one of the following uncontrolled or unstable cardiovascular diseases: stroke, ECG confirmed acute ischemia or myocardial infarction, and/or clinically significant dysrhythmia.

Endpoints

Primary Study Endpoint of Efficacy

The primary outcome will be a composite of symptomatic VTE, VTE-related death, and VTE detected at mandatory bilateral lower limbs venous duplex scan and computed tomography pulmonary angiogram and symptomatic ATE (myocardial infarction (MI), non-haemorrhagic stroke, major adverse limb event (MALE), and cardiovascular (CV) death at day 35 analysed in the ITT population.

Secondary Endpoints of Efficacy

Secondary endpoints are to compare rivaroxaban with standard post-hospital discharge treatment in clinically ill patients at high risk for VTE:

•VTE-related death (death by PE or death in which PE cannot be excluded as the cause) and symptomatic VTE (DVT of the lower extremities and non-fatal PE);

•The composition of symptomatic VTE (DVT of the lower extremities and non-fatal PE) and all-cause mortality;

•The composition of symptomatic VTE (DVT of the lower extremities and non-fatal PE), myocardial infarction (IM), non-haemorrhagic stroke and cardiovascular death (CV) (death from known CV and death in which the CV cause cannot be excluded; by this definition, a VTE-related death is considered a CV death).

Endpoints of Safety

The primary safety endpoint is major bleeding as defined by the International Society of Thrombosis and Haemostasis (ISTH) criteria:
A major bleeding event according to ISTH is defined as evident haemorrhage associated with decrease in haemoglobin levels of 2 g/dl or higher or leading to transfusion of two or more units of red blood concentrate or whole blood, or haemorrhage occurring in a critical site: e.g., intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartmental, retroperitoneal syndrome, or a fatal outcome.
The secondary safety outcomes will be a combination of major bleeding, clinically relevant nom major bleeding and other bleeding, also defined by the ISTH criteria:
Clinically relevant non-significant bleeding is defined as an evident hemorrhage not meeting the criteria of significant bleeding but associated with medical intervention, unscheduled contact (visit or phone call) with a doctor, interruption (temporary) of study treatment, or associated with discomfort to the participant such as pain or impairment of daily activities.
Another bleeding is defined as any other evident haemorrhage that does not meet the ISTH criteria for significant or non-significant clinically relevant haemorrhage.

Data will be disclosed as follows:
Study flow diagram (figure 3)
Baseline characteristics (table 2)
Primary efficacy, safety, secondary efficacy (table 3)
Primary and secondary efficacy (figure 4)
Subgroup analysis (table analysis)

Sample size
The sample size was calculated assuming the power of 80%, a significance level of 0.05, the response anticipated for the occurrence of the primary efficacy endpoint of 15% in the standard of care arm (control group) and 5% of the treatment group, with a relative risk reduction around of 67%. In the MARINER trial[2], the relative risk reduction was 56% for symptomatic VTE events, and on the metanalysis of the 4 extension trials, the relative risk reduction was 40-50%.[3] Given that COVID-19 is a more thrombogenic disease, and we will for first-time computed tomography pulmonary angiogram scans for the primary endpoint, we believe 67% is a realistic expected relative risk reduction for both venous and arterial events. If there is a true difference in favor of the proposed treatment of 10% (15% vs. 5%), then 282 patients are required with a power of 80% that the upper limit of a 95% confidence interval will exclude a difference in favor of the standard group of more than 50%. With a drop-out rate of 10%, a total of 320 patients will be necessary (160 per arm).
Interim Analysis

Beyond the initial sample size calculation, a formal interim analysis by the Data and Safety Monitoring Board (DSMB) evaluating primarily safety may recommend modifications in the sample size. The first formal interim analysis will be performed when the first 200 patients have been enrolled and have completed the 35-day follow-up visit.

Basic principles of statistical analysis

We will use the following definitions of populations:

Intention to Treat (ITT): all the eligible randomized patients according to the group which they have been allocated, regardless of what treatment patients ended up receiving post-randomization.

Per Protocol: limited to patients who followed the protocol. It is defined as the use of rivaroxaban for at least 80% of preconized days among allocated to group treatment, and patients in group control who followed the standard care.

Discontinuation rule

Table 2 describes the discontinuation rule used for per-protocol analysis. For the control group, discontinuation was considered the use of any anticoagulant for the defined timeframe.

≤ 48 hours = no deviation

≥48 hours ≤ 7 days = temporary deviation.

7 days = definitive deviation

For the per-protocol analysis, we considered only definitive deviation.

	Period of treatment arm migration		
Treatment Arm	≤ 48 hours	≥48 hours ≤ 7 days	> 7 days
Rivaroxaban[1]	XXX	XXX	XXX
Control[2]	XXX	XXX	XXX

Table 2. Treatment/control arm protocol deviation criteria

Baseline variables, primary and secondary outcomes will be analyzed considering ITT population. Baseline characteristics will be presents as described in Table 1 of Appendix A. The statistical analyses will be performed with the software SPSS or Excel.

Primary Outcome of Efficacy Analysis

Using the ITT population, the **relative risk (RR)** or **risk ratio** is the ratio of the probability of an outcome in an exposed group (treatment) to the probability of an outcome in an unexposed group (control). Relative risk measures the association between the exposure and the outcome. Assuming the causal effect between the exposure and the outcome, values of RR can be interpreted as follows:

RR = 1 means that exposure does not affect the outcome.

RR < 1 means that the risk of the outcome is decreased by the exposure, which can be called a "protective factor".

RR > 1 means that the risk of the outcome is increased by the exposure.

Relative risk can be estimated from a 2×2 contingency table:

	Group		
	Treatment	Control	Total
Events	a	b	a+b
Non-events	c	d	c+d
Total	a+c	b+d	N

Where:

a: represents the number of patients who have at least one outcome defined as a **primary outcome of efficacy** during 35 days in the treatment group;

b: represents the number of patients who have at least one outcome defined as a **primary outcome of efficacy** during 35 days in the control group;

c: represents the number of patients who do not have any outcome defined as a **primary outcome of efficacy** during 35 days in the treatment group;

d: represents the number of patients who do not have any outcome defined as a **primary outcome of efficacy** during 35 days in the control group.

The point estimate of the relative risk is

$$\widehat{RR} = \frac{\frac{a}{a+c}}{\frac{b}{b+d}}.$$

The sampling distribution of the is closer to normal than the distribution of RR with standard error

$$SE\left(\ln\left(\widehat{RR}\right)\right) = \sqrt{\left[\left[\frac{1}{a} - \frac{1}{a+c}\right] + \left[\frac{1}{b} - \frac{1}{b+d}\right]\right]}.$$

The 1 confidence interval for the ln(RR) is then

$$CI_{1-2\alpha}(\ln(RR) = \ln(\widehat{RR}) \pm z_{\alpha} SE\big(\ln\big(\widehat{RR}\big)\big),$$

where is the standard score for the chosen level of significance. To find the confidence interval around the RR itself, the two bounds of the above confidence interval can be exponentiated.

Primary hypothesis will be defined as:

$H_0: RR = 1$: exposure does not affect the outcome.

$H_a: RR < 1$: the risk of the outcome is decreased by the exposure.

All patients in the treatment group are compared with all patients in the control group.
The efficacy analysis tests will be one-sided, with a type I error rate of 2.5%, assuming a two-sided 95% confidence interval. The cumulative incidence of the composite of events will be compared between the rivaroxaban and control group, and the **relative risk (RR)** or **risk ratio** will be estimated.

The superiority of the treatment is claimed if the upper limit of 95% confidence interval is less than one.

Primary outcome results will be presented according to Table 2.

For the safety analysis, statistical tests will be two-sided, with a type I error rate of 5% and a two-sided 95% confidence interval.

Secondary Outcomes of Efficacy Analysis

Relative risks will be reported with the respective 95% confidence intervals for Binary outcomes. For continuous outcomes, mean differences between the groups will be reported with the respective 95% confidence intervals. It is intended to present the secondary and safety outcomes according to Tables 4, 5 and 6 of Appendix A.

Sensitivity Analyses

We planned sensitivity analyses with the same principles described for the primary outcome in the ITT population using the Per Protocol population.

6. Adverse Events (AE)

Serious adverse effects (SAE) will be classified and presented according to the following criteria:

1. Fatal (AE that causes or leads to death).

2. Risk to life (puts the patient at immediate risk of death).

3. Demands or prolongs hospitalization.

4. Results in disability.

5. Significant medical event, which may require clinical or surgical intervention to prevent one of the outcomes listed above.

These events will be reported for each group and compared with the chi-square test.

7. Subgroup analysis

Subgroup analysis will be calculated between treatment and control groups according to interest groups: age, BMI, creatinine clearance, modified improve score, d-dimer levels and use of antiplatelets. The sensitive analysis will check p-interactions for each variable for the primary outcome. Table 4 describes the subgroup analysis.

8. Risk and benefit analysis

It is intended to present the Number Needed to Treat (NNT), that is the inverse of the absolute risk reduction (ARR) for two situations: The NNT for the composite primary outcome and the NNT for the combination of pulmonary embolism and cardiovascular death.

We have pre-specified 2 NNT analysis

1. Primary endpoint
2. Symptomatic + fatal VTE

The number needed to harm (NNH) that is the inverse of absolute risk increase will be calculated using major bleeding, which is our key safety outcome.

Appendix A

Tables

Table 1. Modified IMPROVE D score

VTE Risk Factor	Points
Previous VTE	3
Known thrombophilia*	2
Lower-limb paralysis/ paresis	2
History of cancer**	2
Immobilization ≥1 day***	1
ICU/CCU stay	1
Age >60 years	1

Table 1. Modified International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) risk score[19]. *A congenital or acquired condition leading to excess risk of thrombosis (e.g., factor V Leiden, lupus anticoagulant, factor C or factor S deficiency); **Cancer (excluding non-melanoma skin cancer) present at any time in the past 5 years. *** Immobilization is being confined to bed or chair with or without bathroom privileges. VTE: venous thromboembolism; ICU: intensive care unit; CCU: cardiac care unit.

Table 2 – Baseline Characteristics

Characteristics	Treatment (n=)	Control (n=)
Mean age (years)	xx.x ± xx.x	xx.x ± xx.x
Age ≥75 yr — no. (%)	x/x (%)	x/x (%)
Gender - Female, n/total (%)	x/x (%)	x/x (%)
BMI (Kg/m²)	xx.x ± xx.x	xx.x ± xx.x
BMI ≥ 30, n/total (%)	x/x (%)	x/x (%)
Creatinine clearance		
30 to <50 ml/min	x/x (%)	x/x (%)
≥50 ml/min	x/x (%)	x/x (%)
Mean duration of index hospitalization — days	x/x (%)	x/x (%)
ICU or CCU stay — no. (%)	x/x (%)	x/x (%)
Modified IMPROVE VTE risk score — no. (%)		
2-3	x/x (%)	x/x (%)
≥4	x/x (%)	x/x (%)
D-Dimer <500 ng/ml n/total (%)	xx.x [xx.xx; xx.xx]	xx.x [xx.xx; xx.xx]
D-Dimer >500 ng/ml n/total (%)	xx.x [xx.xx; xx.xx]	xx.x [xx.xx; xx.xx]
Antiplatelet, n/total (%)	x/x (%)	x/x (%)

Table 3 – Primary Endpoint and components of the primary outcome.

Outcomes	Group		Relative risk (95%CI)
	Treatment	Control	
	(n = xxx)	(n = xxx)	x.xx (x.xx – x.xx)
Primary outcome	xxxx	xxxx	x.xx (x.xx – x.xx)
Composite of composite of symptomatic VTE, VTE-related death, asymptomatic VTE detected at duplex scan and computed tomography pulmonary angiogram and symptomatic ATE (myocardial infarction (MI), non-haemorrhagic stroke, major adverse limb event (MALE), and cardiovascular (CV) death at day 35.	xxxx	xxxx	x.xx (x.xx – x.xx)
Symptomatic DVT	xxxx	xxxx	x.xx (x.xx – x.xx)
Symptomatic PE	xxxx	xxxx	x.xx (x.xx – x.xx)
Fatal PE	xxxx	xxxx	x.xx (x.xx – x.xx)
Asymptomatic DVT detected at duplex scan	xxxx	xxxx	x.xx (x.xx – x.xx)
Asymptomatic PE detected at computed tomography pulmonary angiogram	xxxx	xxxx	x.xx (x.xx – x.xx)
Symptomatic arterial thrombosis			x.xx (x.xx – x.xx)
Myocardial infarction	xxxx	xxxx	x.xx (x.xx – x.xx)
Non-haemorrhagic stroke	xxxx	xxxx	x.xx (x.xx – x.xx)
Major adverse limb event (MALE)	xxxx	xxxx	x.xx (x.xx – x.xx)
Cardiovascular deaths	x.xx		
	[x.xx - x.xx]		

Table 4 – Secondary Endpoints

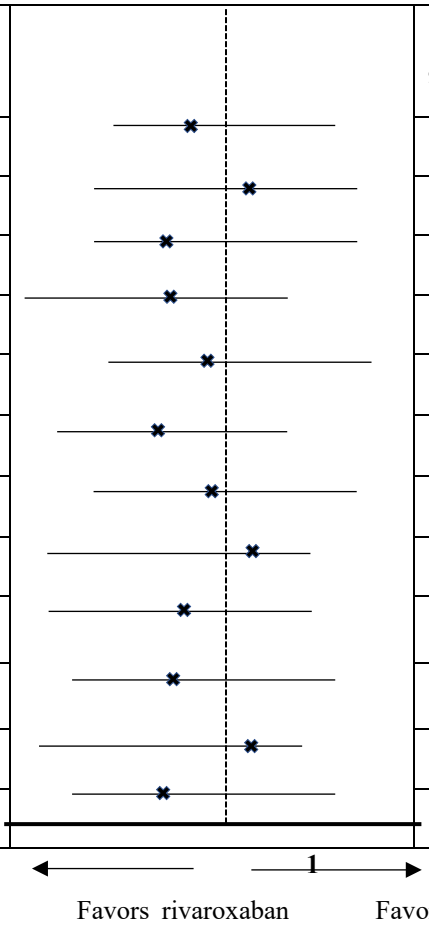
Outcomes	Group		Relative risk (95%CI)
	Treatment	Control	
	(n = xxx)	(n = xxx)	x.xx (x.xx – x.xx)
Secondary efficacy outcomes	xxx	xxx	x.xx (x.xx – x.xx)
Symptomatic and fatal VTE	xxx	xxx	x.xx (x.xx – x.xx)
Symptomatic VTE and Death from any cause			
A composite of MI, stroke, failure, VTE, and cardiovascular death	xxx	xxx	x.xx (x.xx – x.xx)

Table 5 - Safety endpoints.

Variables	Treatment n =	Control n =	Relative risk (95%CI)
ISTH Major bleeding	x/x (%)	x/x (%)	x.x [x.x - x.x]
Decrease in hemoglobin ≥ 2g/dl	x/x (%)	x/x (%)	x.x [x.x - x.x]
Need for transfusion	x/x (%)	x/x (%)	x.x [x.x - x.x]
Critical bleeding*	x/x (%)	x/x (%)	x.x [x.x - x.x]
Fatal bleeding	x/x (%)	x/x (%)	x.x [x.x - x.x]
Major bleeding or clinically relevant bleeding	x/x (%)	x/x (%)	x.x [x.x - x.x]
Clinically relevant bleeding	x/x (%)	x/x (%)	
Minor	x/x (%)	x/x (%)	
Any bleeding	x/x (%)	x/x (%)	x.x [x.x - x.x]

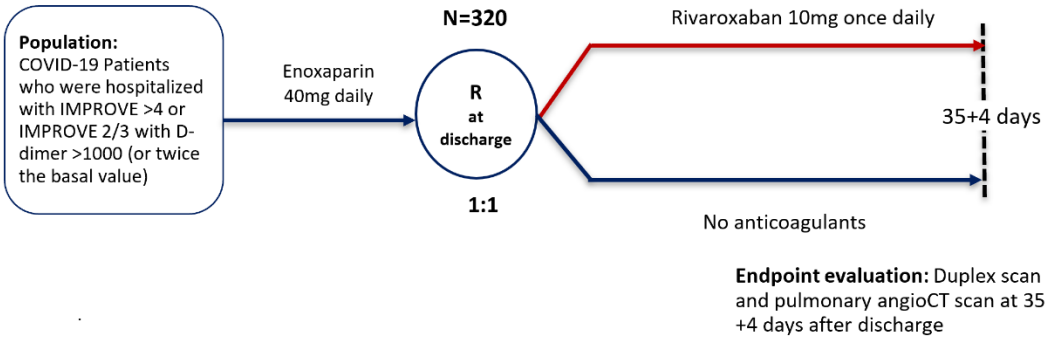
Table 6. Subgroup analysis

Subgroup		**Rivaroxaban (n=xxx)**	**Control (n=xxx)**	**RR (CI 95%)**
Age (yrs)	≤60			
	≥60			
BMI	≤30			
	≥30			
Creatinine Clearance ml/min	30 to <50 ml/min			
	≥50 ml/min			
Modified IMPROVE VTE risk score	2-3			
≥4	≥4			
D-Dimer level above the UNL	≥500 ng/ml			
	≥500 ng/ml			
Antiplatelets use — no. (%)	no			
	yes			



Figures

Figure 1. Study design



Efficacy Endpoint: A composite of symptomatic VTE, VTE-related death or VTE detected at mandatory bilateral lower limbs venous duplex scan + pulmonary CT scan at day 35+4 and symptomatic arterial thromboembolism (myocardial infarction (MI), non-hemorrhagic stroke, major adverse limb events [MALE] and cardiovascular [CV] death in COVID-19 patients with moderate symptoms.

Figure 1. The MICHELLE Trial design. IMPROVED modified International Medical Prevention Registry on Venous Thromboembolism; R: randomization; VTE: venous thromboembolism; CTPA: computed tomography pulmonary angiogram.

Figure 2. Trial visit schedule

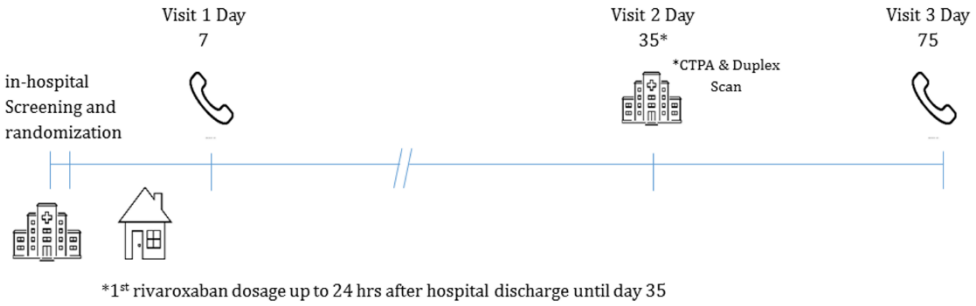


Figure 2. The MICHELLE Trial visit schedule. CTPA: computed tomography pulmonary angiogram.

Figure 3. Study-flow diagram

Michelle Trial Consort Diagram

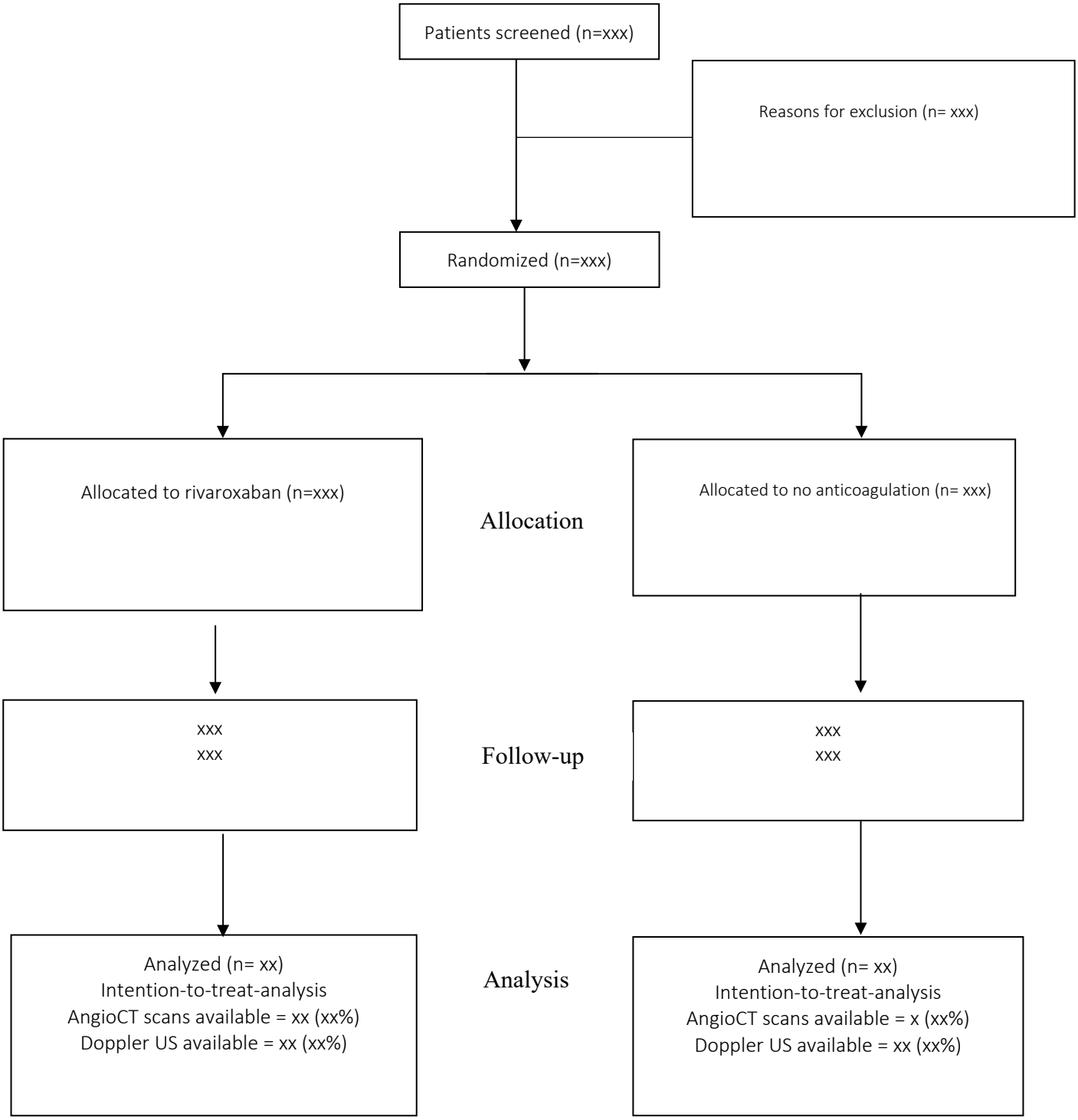
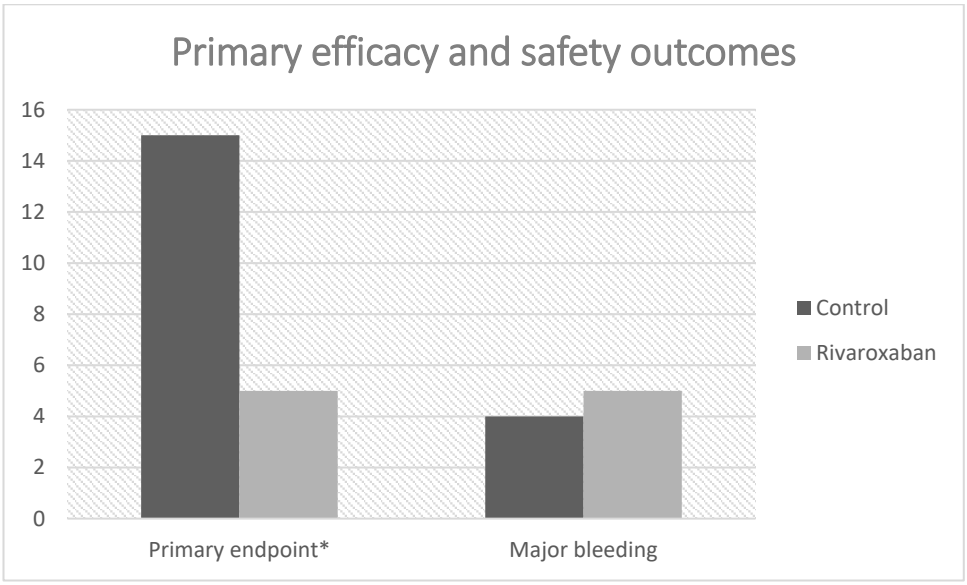


Figure 4. Primary efficacy outcomes bar graph


Primary efficacy and safety outcomes
16
14
12
10
8
6
4
2
0
Primary endpoint*
Major bleeding
Control
Rivaroxaban

Final Study Protocol

CLINICAL STUDY PROTOCOL

Evaluation of rivaroxaban *versus* standard treatment in clinically ill patients with COVID-19 to reduce the risk of post-discharge thromboembolism (The MICHELLE study)

Version No: 2.0
Date: April 1, 2021

Confidentiality statement
The information in this document contains exclusive or confidential trade secrets and information and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be aware that it is unique or confidential information and that it cannot be disclosed. These disclosure restrictions will also apply to all future information provided to you that is indicated to be unique or confidential

Declaration of Conformity to Good Clinical Practice (BPC)
This study will be conducted in accordance with the BPC and the appropriate regulatory requirements.

GENERAL INFORMATION

Sponsor	*Science Valley Research Institute*, supported by a researcher-initiative study by Bayer SA
Main Investigator	Eduardo Ramacciotti
Technical support	*Science Valley Research Institute*

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Summary

SYNOPSIS OF THE PROTOCOL

Title of the study	Rivaroxaban evaluation versus standard treatment in clinically ill patients with COVID-19 to reduce the risk of post-discharge venous and arterial thromboembolism (The MICHELLE STUDY) MICHELLE comes from the Acronym: **M**edically Ill hospitalized patients for Covid - t**H**rombosis **E**xtended proph**L**axis with rivaroxaban th**E**rapy: The MICHELLE Trial.
Study design	This is a multicenter, prospective, randomized, open-label, controlled study.
Description of the compound	Rivaroxaban (BAY 59-7939), ATC code = B01AF01 (direct Factor Xa inhibitors).
General objectives	The main objective is to evaluate the efficacy and safety of rivaroxaban compared to standard treatment in patients clinically ill with COVID-19 discharged from the hospital at high risk for cardiovascular events.
Primary efficacy outcomes	The primary efficacy outcome is a combination of symptomatic venous thromboembolism (VTE: deep vein thrombosis [DVT] of the lower extremities and non-fatal pulmonary embolism [PE]) and VTE-related death (death by and or death in which VTE cannot be excluded as the cause) in combination with asymptomatic VTE (detected by Doppler ultrasound of the lower limbs and pulmonary angiotomography performed on day 35±4 after hospital discharge), in addition to acute myocardial infarction [MI], non-hemorrhagic stroke, major adverse limb event (arterial ischemia) or cardiovascular death
Secondary Efficacy outcomes	Secondary endpoints are to compare rivaroxaban with standard post-hospital discharge treatment in clinically ill patients at high risk for VTE: •VTE-related death (death by PE or death in which PE cannot be excluded as the cause) and symptomatic VTE (DVT of the lower extremities and non-fatal PE); •The composition of symptomatic VTE (DVT of the lower extremities and non-fatal PE) and all-cause mortality;

	•The composition of symptomatic VTE (DVT of the lower extremities and non-fatal PE), myocardial infarction (IM), non-hemorrhagic stroke and cardiovascular death (CV) (death from known CV and death in which the CV cause cannot be excluded; by this definition, a VTE-related death is considered a CV death).
Exploratory Objectives	Exploratory objectives are to compare rivaroxaban with standard treatment in the following post-hospital discharge results in clinically ill patients with COVID-19 at high risk of VTE in relation to the panel of procoagulant and inflammatory biomarkers (PCR, D-dine, IL-6, IL-17, microparticles, PAI-1 and thrombomodulin).
Safety outcomes	The primary safety endpoint is major bleeding, as defined by the International Society of Thrombosis and Hemostasis.
Secondary safety outcomes	The secondary safety outcome is a combination of major bleeding, significant non major bleeding and other bleeding using the hemorrhage criteria validated by the International Society on Thrombosis and Hemostasis (ISTH)
Hypothesis	The primary hypothesis is that rivaroxaban is superior to standard treatment in preventing the composition of symptomatic VTE (DVT of the lower extremities and non-fatal PE) and death related to VTE (death by PE or death in which PE cannot be excluded as the cause) in combination with asymptomatic VTE (detected by Doppler ultrasound of the lower limbs and pulmonary angiotomography) performed post-hospital discharge in addition to acute myocardial infarction, non-hemorrhagic stroke, major adverse limb event (arterial ischemia) or cardiovascular death in patients clinically ill with COVID-19 discharged from the hospital at high risk for VTE.
Overview	This is a multicenter, prospective, randomized, open, controlled by standard treatment, designed to evaluate rivaroxaban compared to standard treatment in the prevention of symptomatic VTE events (DVT of the lower extremities and non-fatal PE) and Deaths related to VTE

	(death by PE or death in which PSE cannot be excluded as the cause), also in a period of 35±4 days after hospital discharge. The study consists of an open treatment phase of 35±4 days and a safety follow-up period of thirty days. The population of participants is composed of men and women aged 18 years or older who completed screening no later than one day after leaving the hospital and who were hospitalized due to the new onset or exacerbation of COVID-19. Initial hospitalization should last for at least three consecutive days. To be eligible, participants must have a higher risk of VTE, demonstrated by a modified total risk score by the International Registry on Medical Prevention in Venous Thromboembolism (IMPROVE) of: •≥ 4; •3 with d-dimer ≥ UNL or •2 with d-dimer ≥ UNL In addition, participants will need to have received treatment during initial hospitalization with LMWH, fondaparinux, or UFH at prophylactic doses. Any patient with a clinical picture requiring the use of any parenteral or oral anticoagulant (e.g., atrial fibrillation) during the study will not be eligible for participation. In addition, patients at a particularly increased risk of bleeding and those who use medications that may interact with the drug study will be excluded. Participants who meet all inclusion criteria and at no Exclusion criteria will be randomly assigned to receive rivaroxaban or standard treatment. Randomization should occur on the same day that the participant leaves the hospital or the following day, and may occur in the hospital, clinic, or other post-discharge destination. After randomization, participants will receive open treatment with 10 mg rivaroxaban daily or standard treatment. Standard treatment was chosen as a comparator due to current guidelines that do not yet recommend thromboprophylaxis in clinically ill patients after hospital discharge. The first dose of the drug study should be administered no later than one day after the participant leaves the hospital and as soon as possible after randomization. Participants will be instructed to discontinue the drug study after taking a dose on day 35±4 and to make a treatment-ending visit within four days. Regardless of the day on which the visit of day 35±4 occurs, no medication in the study can be taken after day 35±4. The participant will be evaluated 35±4 days later for

	security follow-up. This will be the last contact with the participant, unless extended security monitoring is required. If a participant is suspected to have an efficacy or bleeding outcome event during the study, the doctor who performs the treatment should exercise clinical judgment and follow the guidelines established to apply the standard of care. Disclosure of the drug study should not be necessary. Anticoagulant regimens do not require adjustment in this study. There is no specific reverse agent for rivaroxaban; the treatment of a participant with hemorrhagic event should not be influenced by the knowledge of the drug in the treatment study. Rivaroxaban will not be provided to participants after completing the treatment of the study, unless required by local regulations. Randomization in this study is preceded by hospitalization due to an acute COVID-19 disease and the treatment phase with the study drug extends for 35±4 days after randomization, to correspond to the period of higher risk of VTE. Chronic therapy with the study drug is not being tested. The primary efficacy result is the composition of all events of symptomatic VTE (DVT of the lower extremities and non-fatal PE) and death related to VTE (death by PE or death in which PE cannot be excluded as the cause), in combination with a Doppler ultrasound of the lower limbs and pulmonary angiography performed after hospital discharge) in addition to acute myocardial infarction, non-hemorrhagic stroke, major adverse limb event (arterial ischemia) or cardiovascular death in patients clinically ill with COVID-19 discharged from the hospital at high risk for VTE from randomization until day 35±4. The main safety outcome for this study major bleeding according *to the International Society of Thrombosis and Hemostasis* (ISTH). It is estimated that, in total, approximately 320 participants are randomized for rivaroxaban or standard treatment in a ratio of 1:1. For exploratory analyses of biomarkers in this population, two blood samples will be collected - at the randomization visit and at the follow-up visit of day 35±4. For this study, an Executive Committee (EC), an Independent Data Monitoring Committee (IDMC) and a Clinical Events Committee (CEC) will be appointed. All committees will be governed by separate letters.
Study population	

	The population of participants is composed of men and women aged 18 years or older, who completed screening no later than one day after leaving the hospital and who were hospitalized due to a new onset or exacerbation of COVID-19. Initial hospitalization should last for at least three consecutive days. To be eligible, participants must test positive on the reverse transcriptase-polymerase chain reaction (RT-PCR) test for SARS-CoV-2 in a respiratory tract sample. Patients should have a higher risk of VTE, demonstrated by a modified total VTE risk score by the International Registry on Medical Prevention in Venous Thromboembolism (IMPROVE) of: • ≥ 4; •2-3 with d-dimer ≥ upper normal limit (UNL) In addition, participants should have received treatment during initial hospitalization with low molecular weight heparin (LMWH), fondaparinux, or unfractionated heparin (UFH) at standard prophylactic doses. Any patient with a clinical presentation requiring parenteral or oral anticoagulant (e.g., atrial fibrillation, another clinical picture) during the study will not be eligible for participation. In addition, patients at a particularly increased risk of bleeding and those using medications that interact with the drug study will be excluded.
Dosage and Administration	The treatment groups in this study are rivaroxaban and standard treatment. Participants will be randomly assigned in a 1:1 ratio to receive 10 mg of rivaroxaban daily or no anticoagulation. The first dose of the drug study should be administered no later than one day after the participant leaves the hospital and as soon as possible after randomization. The date and time of the first dose of the study drug and the last dose of LMWH and UFH should be recorded as precisely as possible. The first dose of the product in the study should be administered under supervision, so it should not be delayed. All participants should take the drug from the rivaroxaban study or no anticoagulant - standard treatment daily, with or without food, at approximately the same time each day and discontinue the drug study after taking the dose on day 35±4. Regardless of the day on which the visit of day 35±4 occurs, no medication in the study can be taken after day 35±4.

	A missed dose should be taken as soon as possible (up to eight hours before the next scheduled dose) and the next scheduled dose should be taken on a regular basis. We chose not to use placebo in patients with COVID-19 and to keep the study open for the safety of study participants.
Interruption of Study Medication	The study drug may be temporarily discontinued, if necessary, for invasive procedures or according to medical needs (e.g. at the time of a bleeding event or need for prohibited therapy). If a participant is hospitalized for any reason other than a VTE or bleeding-related event, the study drug should be discontinued during hospitalization unless the doctor performing the treatment considers that the use of an anticoagulant is clinically justified. Participants may use an appropriate anticoagulant at the discretion of the doctor who performs the treatment. In this case, the study drug should be temporarily discontinued and may be restarted upon discharge from the participant and at the discretion of the investigator. These interruptions will be recorded in electronic clinical records (eCRF). During the treatment period, if the participant develops any clinical picture that, at the discretion of the investigator, requires anticoagulant thromboprophylaxis or long-term fibrinolysis, the treatment of the study will be temporarily discontinued or permanently discontinued, and the participant will be treated as deemed appropriate by the physician who attends it. The participant will be asked to continue the study so that he/she can be monitored for efficacy and safety results.
Evaluations / Efficacy Results	The primary efficacy outcome is the composition of all events of symptomatic VTE (DVT of the lower extremities and non-fatal PE) and VTE-related death (death by PE or death in which PE cannot be excluded as the cause) in combination with asymptomatic VTE (detected by Doppler ultrasound of the lower limbs and pulmonary CT angiography) performed after hospital discharge in addition to acute myocardial infarction, non-hemorrhagic stroke, major adverse limb event (arterial ischemia) or cardiovascular death in patients clinically ill with COVID-19 discharged from the hospital at high risk for VTE. The secondary efficacy results are as follows:

	Secondary endpoints are to compare rivaroxaban with standard post-hospital discharge treatment in clinically ill patients at high risk for VTE: •VTE-related death (death by PE or death in which PE cannot be excluded as the cause) and symptomatic VTE (DVT of the lower extremities and non-fatal PE); •The composition of symptomatic VTE (DVT of the lower extremities and non-fatal PE) and all-cause mortality; •The composition of symptomatic VTE (DVT of the lower extremities and non-fatal PE), myocardial infarction (IM), non-hemorrhagic stroke and cardiovascular death (CV) (death from known CV and death in which the CV cause cannot be excluded; by this definition, a VTE-related death is considered a CV death). Exploratory evaluation of procoagulant and inflammatory biomarkers (PCR, D-dimers, IL-6, IL-17, microparticles, PAI-1 and thrombomodulin). Any clinical event that suggests the possibility of an efficacy outcome event (including acute coronary syndrome [ACS] and temporary ischemic crisis [ITC]) will be submitted for evaluation. If a participant is suspected to have an efficacy outcome event during the study, the physician who performs the treatment should exercise his/her clinical judgment and follow the guidelines established by the institution to apply the standard of care. The development of the drug in the study should not be necessary, as anticoagulant regimens do not require adjustment, regardless of the use of standard treatment vs. rivaroxaban, when administered at the doses used in this study.
Safety Assessments / Results	The main safety outcome is major bleeding using hemorrhage criteria validated according to ISTH. Other safety findings are clinically relevant non-significant hemorrhage and other bleeding. An important hemorrhagic event according to ISTH is defined as evident hemorrhage associated with: decrease in hemoglobin levels of 2 g/dl or higher, or leading to transfusion of two or more units of red blood concentrate or whole blood, or hemorrhage occurring in a critical site: e.g., intracranial, intraspinal[1], intraocular, pericardial, intraarticular, intramuscular with compartmental, retroperitoneal syndrome, or a fatal outcome. Clinically relevant non-significant hemorrhage is defined as an evident hemorrhage not meeting the criteria of

	significant bleeding, but associated with medical intervention, unscheduled contact (visit or phone call) with a doctor, interruption (temporary) of study treatment, or associated with discomfort to the participant such as pain or impairment of daily activities. Another hemorrhage is defined as any other evident hemorrhage that does not meet the ISTH criteria for significant or non-significant clinically relevant hemorrhage. Any clinical event that suggests the possibility of an event occurring as a result of bleeding will be sent for evaluation. If a participant presents a serious bleeding event during treatment with the study drug, routine measures should be considered. Security in general will also be evaluated.
Statistical Methods	Main set of analysis and analysis phase: •Intent of treatment (ITT): this set of analysis consists of all randomized participants who have a signed and valid free and informed consent form; and •Until day 35±4: this analysis phase includes all randomization data up to day 35±4 (inclusive). Sample size calculation The sample size was calculated assuming the power of 80%, a significance level of 0.05, the response anticipated for the occurrence of the primary efficacy endpoint of 15% in the standard of care arm (control group) and 5% of the treatment group, with a relative risk reduction around of 60%. In the MARINER trial[1], the **relative risk** reduction was 56% for symptomatic VTE events, and on the metanalysis of the 4 extension trials, the relative risk reduction was 40-50%. Given that COVID-19 is a more thrombogenic disease, and we will for first-time computed tomography pulmonary angiogram scans for the primary endpoint, we believe 67% is a realistic expected relative risk reduction for both venous and arterial events. If there is a true difference in favor of the proposed treatment of 10% (15% vs. 5%), then 282 patients are required with a power of 80% that the upper limit of a 95% confidence interval will exclude a difference in favor of the standard group of more than 50%. With a drop-out rate of 10%, a total of 320 patients will be necessary (160 per arm).
Primary efficacy result	

	Using the ITT population, the relative risk (RR) or risk ratio is the ratio of the probability of an outcome in an exposed group (treatment) to the probability of an outcome in an unexposed group (control). Relative risk measures the association between the exposure and the outcome. All patients in the treatment group are compared with all patients in the control group. The efficacy analysis tests will be one-sided, with a type I error rate of 2.5%, assuming a two-sided 95% confidence interval. The cumulative incidence of the composite of events will be compared between the rivaroxaban and control group, and the relative risk (RR) or risk ratio will be estimated. The superiority of the treatment is claimed if the upper limit of 95% confidence interval is less than one. Primary outcome results will be presented according to Table 2. For the safety analysis, statistical tests will be two-sided, with a type I error rate of 5% and a two-sided 95% confidence interval.
Secondary efficacy results (Exploratory)	Each secondary efficacy result will be analyzed based on time from randomization to the first occurrence in the ITT analysis set and analysis phase until day 35±4. The same cox stratified model will be used as well as that of primary efficacy result. Details will be provided in SAP. To control the type I error rate of the family-wise test in 0.05 alpha (two-tailed) in tests for efficacy results, if rivaroxaban superiority over standard treatment in the primary efficacy outcome is established, rivaroxaban superiority over standard treatment in secondary outcomes will be tested sequentially using a closed test procedure in the following hierarchical order, each in alpha of 0.05 (two-tailed): Symptomatic or fatal VTE A composition of symptomatic venous thromboembolism and all-cause mortality A composition of symptomatic venous thromboembolism, myocardial infarction, non-haemorrhagic stroke, and cardiovascular death (death from known cardiovascular disease and death in which the cardiovascular disease cause cannot be excluded).
Safety analysis	
Bleeding results	

	Using ITT analysis, major bleeding events up to day 35±4 relative risks will be reported with the respective 95% confidence intervals for binary outcomes. For continuous outcomes, mean differences between the groups will be reported with the respective 95% confidence intervals. The same analysis will be carried out for the secondary safety analysis, a combination of major, clinically relevant non major and another bleeding.
Risk-benefit analysis	The risk-benefit of rivaroxaban vs. standard treatment will be assessed based on the excess number of events between treatments for events to be prevented (benefits) and events that may be caused (risks).

SCHEDULE OF SCHEDULES AND EVENTS

Protocol activity	Sorting[the]	Randomize[b]	Thirty-day follow-up		
	triage	Day 1	Day 7	Day 35±4 EOT[c]	Day 60 Eos
	Hospital/ clinic/ high target	Hospital/ clinic/ high target	Clinic/ High destination/ telephone	Clinic/ high target	Clinic/ High destination/ telephone
period			-2/+5d	-0/+4D	-5/+5D
Free and informed consent[d]	X				
Inclusion/exclusion[and]	X	X			
Risk of VTE[and]	X	X			
Physical examination and vital signs[f]	X				
Demographics	X				
Medical history	X				
Hemoglobin/platelet count[g]	X				
Serum creatinine[g]	X				
Serum pregnancy test h	X				
D-dimer (local)[i] + biomarkers	X			X	
Computed tomography angiography with chest contrast				X	
Doppler ultrasound of limbs				X	
Distribute the study medicine		X			
Initial hospitalization		X			
Use of LMWH/HNF		X			
Clinical evaluation		X		X	
Symptom assessment			X	X	X

Protocol activity	**Sorting[the]**	**Randomize[b]**	**Thirty-day follow-up**		
	triage	**Day 1**	**Day 7**	**Day 35±4 EOT[c]**	**Day 60 Eos**
	Hospital/ clinic/ high target	**Hospital/ clinic/ high target**	**Clinic/ High destination/ telephone**	**Clinic/ high target**	**Clinic/ High destination/ telephone**
period			-2/+5d	-0/+4D	-5/+5D
Advice from participants [k]		X	X	X	
Contability of the study drug				X	
Clinical status/suspected results			X	X	X
Adverse events	X	X	X	X	X
Concomitant medications	X	X	X	X	X

Legend: EOS = end of the study; TeOT = end of treatment; HECON = health economy; LMWH = low molecular weight heparin; VTE = venous thromboembolism; UFH = unfractionated heparin.

a) Screening may begin at any time after admission to initial hospitalization and once free and informed consent has been obtained. Initial hospitalization should last for at least three and a maximum of ten consecutive days.

b) Randomization should occur on the same day that the participant leaves the hospital or the following day.

c) The participant will be instructed to discontinue the medicine from the study after taking a dose on day 35±4. ***Regardless of the day on which the visit occurs on the 35±4th, no medicine in the study may be taken after the day 35±4.***

d) Full free and informed consent will still have to be obtained before other study procedures are carried out.

e) Inclusion/exclusion criteria and VTE risk score at screening should be evaluated and verified at randomization.

f) Vital signs include heart rate and blood pressure. The physical examination will be performed at screening or randomization. Clinical evaluation is a focused assessment of the heart, lungs, lower extremities, and neurological state. If the physical examination is conducted on Day 1, clinical evaluation on that day will not be required.

g) Hemoglobin, platelet, and serum creatinine count should be obtained as recently as possible, at least two days before the participant leaves the hospital or later, but before randomization.

h) A pregnancy test will have to be performed on women who may become pregnant, and it may be repeated as indicated or locally required.

(i) The d-din value may be obtained at any time from the beginning of initial hospitalization until randomization; the value obtained closest to the beginning of initial hospitalization should be used. A value of >2 x LSN is required if the VTE risk score is 2 or 3.

j) Chest angiography and doppler venous ultrasound will be performed mandatorily in all participants on day 35 4±of follow-up.

k) Includes training on the signs and symptoms associated with DVT, EP and hemorrhage, and the appropriate response if symptoms develop.

Abbreviations

2/1 t1	Half-life
ACCP	American College of *Chest Physicians*
ACM	*All-cause mortality*
ACS	Acute coronary syndrome
ASA	Acetylsalicylic acid
AUC	Area *under the plasma concentration curve*
AV	Arteriovenous
BP	Blood pressure
CEC	*Clinical Event Committee*
CI	Confidence interval
CICU	Cardiac intensive care unit
Cl	Clearance
C_{max}	Maximum serum concentration
C_{min}	Minimum serum concentration
COPD	Chronic obstructive pulmonary disease
CrCl	Creatinine *clearance*
CT	Computed tomography
CV	Cardiovascular
CYP3A4	Cytochrome P450 3A4
DVT	Deep vein thrombosis
EC	Executive Committee
ECRF	Electronic case *report form*
EF	Ejection fraction
EOS	End of *study*
EOT	End of *treatment*
ER	Emergency room
EU	European Union
FDA	U.S. Food *and Drug Administration*
Fk	Pharmacokinetics
FXa	Factor Xa
GCP	Good clinical practice
HF	Heart *failure*
HF	Congestive heart failure
HR	Risk ratio (*hazard ratio*)
IC	Free and informed consent form
ICH	International Conference on Harmonization

ICU	Intensive care unit
IDMC	Independent data monitoring committee
IEC	*Independent Ethics Committee*
IMPROVE	*International Medical Prevention Registry on Venous Thromboembolism*
IRB	Research Ethics Committee
ISTH	International *Society of Thrombosis and Haemostasis (International Society of Thrombosis and Haemostasis*)
ITT	Intention-to-treat
Ka	Constant first-order absorption rate
LC-MS/MS	Liquid *chromatography coupled to tandem mass spectrometry*
LDUH	Low-dose *unfractionated heparin*
LMWH	Low molecular weight heparin
LVEF	Left ventricular ejection fraction
MedDRA	*Medical Dictionary for Regulatory Activities*
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NT-proBNP	N-terminal pro-hormone natriuretic peptide
P2Y12	Purinergic P2Y receptor coupled to G protein
PE	Pulmonary embolism
PP	According to protocol *(per protocol)*
PPI	Proton pump inhibitor
PQC	Complaint about product *quality complaint*
Redcap	Electronic *data capture*
RRR	Relative risk reduction
SAP	*Statistical analysis plan*
SUSAR	Suspected unexpected serious adverse *reaction*
Them	Length of *stay;*
TIA	Temporary ischemic crisis
Tmax	Time to reach maximum concentration in plasma
UFH	Unfractionated heparin
ULN	Upper limit of normality
USA	United States of America
V/F	Volume of distribution
VTE	Venous thromboembolism

Introduction

Rivaroxaban is an oral factor Xa inhibitor anticoagulant that has been developed for the treatment of several diseases mediated by thrombosis, an extremely frequent global disease. [2-5] Rivaroxaban is marketed under the trade name XARELTO® and has been approved for multiple indications worldwide. [5] The clinical development program for rivaroxaban is extensive, covering several indications and containing more than 70,000 participants in phase 1 studies up to several and wide phase 4 studies. [1,5,6] More than 40,000 of these participants were exposed to rivaroxaban in completed and ongoing interventional clinical studies and in non-interventional studies, with total daily doses of rivaroxaban ranging from 5 mg to 60 mg. [5] In addition, rivaroxaban (10 mg daily) was evaluated for thromboprophylaxis in clinically ill patients in the MAGELLaN[6] to the extent of the MARINER study. [1]

Background

COVID-19 has caused a large number of thromboembolic events, reaching up to 50% of hospitalized patients. Interestingly, a large number of patients affected by COVID-19 have marked d-dimer elevations, even at the time of hospital discharge, which has caused apprehension in the clinicians who are accompanying them. [7]
Clinically ill patients, i.e., patients who are hospitalized for the treatment of clinically acute diseases, are at high risk of developing VTE during hospitalization and immediately after hospital discharge. [8]Evidence-based clinical practice guidelines from the American College of Thoracic Medicine (ACCP) currently recommend anticoagulant thromboprophylaxis for clinically ill hospitalized acute patients at increased risk of thrombosis for 6 to 21 days. Until complete mobility is recovered or until discharge from the hospital, which is the first. In the US and many other countries including those in Europe, there is a growing trend towards reducing hospital admissions. Although continued thromboprophylaxis with parenteral agents after hospital discharge can potentially reduce the risk of VTE in general, this approach has not yet been widely used, probably due to the challenges in administering parenteral medication by the patient or caregivers and the lack of convincing benefit-risk data with existing anticoagulants. [9] The duration of thromboprophylaxis is largely determined by the duration of hospitalization and currently post-hospital thromboprophylaxis with parenteral agents is not frequently used, despite the fact that the risk of VTE persists after hospital discharge. [10] risk of VTE persists well beyond hospital discharge, studies of extended thromboprophylaxis with oral anticoagulants in post-hospital discharge patients hospitalized for clinical conditions at risk of VTE are justified. This incidence seems to be even higher in patients affected by COVID-19. [7]
In the MARINER[1] which included 12,000 patients and compared rivaroxaban to placebo for extended VTE prophylaxis in patients hospitalized for clinical disease, a 56% reduction in symptomatic events without increased bleeding was observed.

The proposed phase 3, multicenter, prospective, randomized, open- and controlled by standard treatment, it was designed to evaluate rivaroxaban, compared to standard treatment, in the prevention of symptomatic VTE events (DVT of the lower extremities and non-fatal EP) and Deaths related to VTE (death by EP or death in which PE cannot be excluded as the cause) in combination with asymptomatic VTE (detected by Doppler ultrasound of the lower limbs and pulmonary angiography) performed 35±4 days after

hospital discharge in addition to acute myocardial infarction, non-hemorrhagic stroke, major adverse limb event (arterial ischemia) or cardiovascular death in participants aged ≥ 18 years who were hospitalized due to COVID-19 and who present other risk factors for VTE. Prior to randomization, all participants must have been prescribed thromboprophylaxis with low molecular weight heparin (LMWH) or non-fractional heparin (UFH) during initial hospitalization. If the doctor who performs the treatment believes that additional post-hospital discharge therapy with any anticoagulant is clinically indicated, the patient will not be eligible for study participation.

Composite profile

As part of the prothrombin complex, FXa directly converts prothrombin into thrombin. Thrombin converts fibrinogen into fibrin and activates platelets leading to clot formation. The FXa occupies an important space in the coagulation cascade, since it is at the confluence of the intrinsic and extrinsic coagulation pathway, and is the main amplification point for thrombin generation. An FXa molecule is capable of generating more than 1,000 thrombin molecules due to the amplification nature of the coagulation cascade. Selective FXa inhibitors can terminate the amplified burst of thrombin generation and prevent clot generation. [5]
Rivaroxaban is an oral, direct FXa inhibitor anticoagulant. Rivaroxaban is rapidly absorbed after oral administration, with a peak of plasma concentrations occurring approximately 2 to 4 hours post-dose. Rivaroxaban elimination routes include the hepatic pathway and renal pathway. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy young participants and 11 to 13 hours in healthy elderly participants (age 65 to 83 years). There are some clinically relevant drug interactions due to the multiple routes of elimination of rivaroxaban[11].
Rivaroxaban has been developed and approved for the treatment of several diseases mediated by thrombosis. The clinical development program for rivaroxaban is comprehensive, having studied more than 70,000 participants, and includes data from clinical studies and post-marketing surveillance. Rivaroxaban is marketed under the trade name XARELTO®.

2.COMMITTEES

2.1. Executive committee

The executive committee (EC) consists of members of the study's academic leadership. Ad hoc members may *be designated* as needed. The EC has full responsibility for the design, conduction and reports of the study. The EC will monitor safety in general during the study and will receive any recommendations from CIMD regarding possible additional analyses or modifications to the study and decide whether to accept them. The EC will oversee the implementation of any modifications to the study and publication of the results.

2.1.2 Independent Data Monitoring Committee (IDMC)

A IDMC will be established to monitor the progress of the study and ensure that the safety of participants recruited in the study is not compromised. The IDMC will include, among others, a clinical president, physician(s) with experience in clinical studies, but who is not participating in this study and, at least, a statistician. In this letter, details of

IDMC's composition, functions, responsibilities, and processes will be documented. IDMC will review the results of planned partial analyses and make a recommendation on whether the study should be continued as planned, modified, or finalized early due to inefficacy or safety

2.1.3 Committee of Clinical Events

The Clinical Events Committee (CEC) is composed of medical experts eligible by the board or certified by the board as appropriate and necessary. Committee members do not directly include study participants, are not involved in monitoring the MICHELLE study, and have no direct operational responsibilities for conducting the study. Members will analyze all suspected outcome events as described below that occurred after randomization as soon as they become available and evaluate and classify consistently and impartially, according to the definitions in the CPB chart, remaining blind in relation to the assignment of treatment: symptomatic VTE, VTE-related death, asymptomatic VTE (Doppler and AngioCT scan) and symptomatic ATE, MI, non-hemorrhagic stroke, (MALE), and cardiovascular death at day 35.
The CEC will also evaluate bleeding events (major, clinically relevant non-major and another bleeding according to ISTH criteria).

3. PARTICIPANTS

Screening may begin at any time after admission for initial hospitalization and once free and informed consent has been obtained. If a participant's situation changes (including laboratory results or receipt of additional medical records) after screening, but before randomization, in such a way that he or she no longer meets all eligibility criteria, the participant should not be randomized.
The inclusion and exclusion criteria to include participants in this study are described in the following two subsections. If there is any doubt about the inclusion or exclusion criteria below, the researcher should consult the appropriate EC representative before including a participant in the study. Exemptions will not be granted for the participation of the study.

3.1Inclusion criteria

Each potential participant needs to meet all of the following criteria to be included in the study:
1) The participant must be a male or woman aged ≥ 18 years.
2) The reason for hospitalization needs to be a new diagnosis or exacerbation COVID-19, with evidentiary test of SARS-CoV-2 infection based on locally acceptable guidelines. The duration of initial hospitalization should have been at least three consecutive days and is defined as a continuous period of time in an acute care facility (including hospital, observation unit, ER and/or transfer unit; collectively called "hospitals"). The first day that the participant stays any part of the day in the hospital will be counted when determining the duration of initial hospitalization, but the day on which the patient leaves the hospital will not be counted.
3) The participant must have an increased risk of VTE according to the modified total vTE risk score by the IMPROVE Registry (Table 1; modified by Spyropoulos[7)] evaluatedat screening and verified at randomization.
3.a) If the total modified VTE risk score by the IMPROVE Registry is ≥ 4, the participant meets this inclusion criterion.

3.b) If the modified total VTE risk score by the IMPROVE Registry is 2 or 3, it is necessary to obtain a D-dimer value > UNL after the beginning of the initial hospitalization and before randomization.

Risk factor of VTE	**VTE risk score**
previous VTE	3
Thrombophilia known[to]	2
Paralysis or paresis of the lower limb[b]	2
History of cancer[c]	2
ICU/UTC admission	1
Complete immobilization[d] ≥1 day	1
Age ≥ 60 years	1

Table 1: Modified score of the VTE risk factor by the IMPROVE Registry. UTC = cardiac therapy unit; ICU = intensive care unit; VTE = venous thromboembolism.
a: A congenital or acquired disease that leads to excessive risk of thrombosis (e.g., Leiden factor V, anticoagulant lupus, factor C or Factor S deficiency).
b: The leg falls to bed in five seconds, but makes some effort against gravity (taken from the stroke scale of the *National Institutes of Health*[20]).
c: Cancer (excluding non-melanoma skin cancer) present at any time in the last five years (the cancer needs to be in remission to meet the eligibility criteria)
d: Immobilization consists of being confined to the bed or chair, with or without sanitary privilege.
and. Life expectancy of at least three months.
F. Prescription of thromboprophylaxis (according to ACCP guidelines)20 with UFH or LMWH (e.g., dalteparin and enoxaparin) not exceeding 15,000 U on any given day for HNP and not exceeding 5,000 U on any given day for LMWH.
g. Each participant must sign a free and informed consent form (ICF) indicating that he/she understands the objective and procedures necessary for the study and that he/she is willing to participate in the study.

3.2. Exclusion criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

Criteria related to the risk of bleeding:
1) Any hemorrhage (defined as hemorrhage requiring hospitalization, transfusion, surgical intervention, invasive procedures, occurring in an anatomically critical site, or causing disability) within three months before randomization or occurring during the initial hospitalization period.
2) Major surgery, parenchymal organ biopsy, ophthalmic surgery (excluding cataract surgery) or serious trauma (including head trauma) within four weeks prior to randomization.
The investigator's criterion should be applied, but the following guidelines can be considered for the purpose of this study:
Major surgeries often involve opening one or more major body cavities: the abdomen, chest, or skull, and can stress vital organs. Major surgeries are usually performed using general anesthesia in a hospital operating room by a surgeon (or surgeons) and usually require admission for at least one night in the hospital after surgery.

On the other hand, with minor surgeries, the main body cavities are not opened. Minor surgeries may involve the use of local, regional or general anesthesia and can be performed in the emergency room, in an outpatient operating room, or in a clinical office. Vital organs are usually not stressed and surgery can be performed by a single doctor, who may or may not be a surgeon. In general, the person can return home on the same day that minor surgery is performed.
The investigator's criteria should be applied, but fracture or concussion should be considered serious head trauma, although external trauma without fracture or concussion may be considered for inclusion.
3) Any major planned surgery (see exclusion criterion #2) or important invasive diagnostic procedure provided for during the clinical study.
4) Participants with any known coagulopathy or hemorrhagic diatesis or an international normalized ratio (INR) > 1.5 during initial hospitalization without a subsequent value (the last value before randomization) that is ≤ 1.5.
5) A history of hemorrhagic stroke or any intracranial hemorrhage at any time in the past, evidence of primary intracranial hemorrhage on CT or MRI imaging of the brain, or clinical presentation consistent with intracranial hemorrhage. This also applies to participants hospitalized due to ischemic stroke at randomization.
Participants with hemorrhagic transformation of an ischemic infarction prior to randomization are not excluded unless there is evidence of parenchyma hemorrhage (types HP-1 and HP-2):
Hemorrhagic infarction type 1 (IH-1) is defined as a small petechiae along the margins of the infarction and type 2 IH (IH-2) is defined as more confluent petechiae within the infarcted area, but without expansive effect. HP type 1 (HP-1) is defined as hematoma in ≤ 30% of the infarct area with some mild expansive effect; HP type 2 (HP-2) is defined as dense hematoma > 30% of the infarction area with substantial expansive effect or as any hemorrhagic lesion outside the infarction area (Berger, 20012).
Participants with type 1 and IH-2 hemorrhagic infarction are NOT excluded from this study, but participants with HP-1 and HP-2 are excluded from this study.
6) The participant has a history or presence of intracranial neoplasia (benign or malignant), brain metastases, arteriovenous malformation (VA) or aneurysm.
7) Active gastroduodenal ulcer, defined as diagnosed at three months, or current known or symptomatic arteriovenous malformations of the gastrointestinal tract.
8) Platelet count in the screening < 75 x 109 cells/l.
9) Active cancer (excluding non-melanoma skin cancer), defined as cancer that is not in remission or requires active chemotherapy or auxiliary therapies such as immunotherapy or radiotherapy. Chronic hormone therapy (e.g., tamoxifen, anastrozole, leuprolide acetate) is allowed for cancer in remission.
10) Any clinical picture (e.g., atrial fibrillation) requiring the use of any parenteral(s) or oral anticoagulant(s) (e.g., sodic warfarin or vitamin K antagonists, factor II inhibitors or Xa, fibrinolytics) concomitantly with the study drug.
11) Bilateral and unilateral amputation of the lower extremities above the knee.
12) Participant presenting allergy, hyper or known intolerance to rivaroxaban or any of its excipients.
13) Severe renal failure (baseline CrCl < 30 ml/min calculated using the Cockcroft-Gault[1] Section 8.1.2).
14) Known significant liver disease (e.g., acute hepatitis, active chronic hepatitis, cirrhosis) that is associated with coagulopathy or moderate or severe hepatic impairment.
15)Known HIV infection.

16) Uncontrolled systolic blood pressure (BP) maintained ≥ 180 mmHg or diastolic BP ≥ 100 mmHg in randomization despite treatment.
17) Current drug or alcohol abuse, based on the investigator's assessment.
18) Cardiogenic or septic shock with the need for vasopressor(es) or blood pressure support devices during initial hospitalization.
19) Presence of inferior vena cava filter
20) Bronchiectasis or severe cavitary tuberculosis or any other pulmonary condition (e.g., vasculitis) at risk of significant hemoptysis
21) Combined use of P-gp inhibitors and potent CYP3A4 inhibitors (such as ketoconazole, telitromycin or protease inhibitors, among others) in the four days prior to randomization or planned use during the study. The use of itraconazole is prohibited in the seven days prior to randomization and during the study.
22) Combined use of P-gp inducers and cyp3a4 potent inducers (such as, among others, rifampin/rifampicin, rifabutin, rifapentine, phenytoin, phenobarbital, carbamazepine or St. John's wort) in the two weeks prior to randomization or planned use during the study.
23) Received fibrinolysis during initial hospitalization, unless it was received for ischemic stroke at least three whole days prior to randomization.
24) Use of antiplatelet therapy during initial hospitalization, including:
24.a) ASA > 162 mg/day.
24.b) Clopidogrel > 75 mg/day or ticlopidine > 250 mg twice daily.
24.c) Clopidogrel in any dose in combination with omeprazole or esomeprazole.
24.d) > 400 mg/day dipyridamole.
24.e). > 200 mg/day of cilostazol.
24.f) Double therapy with two or more antiplatelet agents (dipyridamole with AAS is allowed).
24.g) Other purinergic P2Y receptor antagonists coupled to G protein (P2Y12) (e.g., prasugrel, ticagrelor).
24.h) Thrombin receptor antagonists (e.g., vorapaxar)
25) Women who may become pregnant without appropriate contraceptive measures, pregnancy or breastfeeding. Before randomization, a woman:
•If you cannot become pregnant: you must be in the pre-menarche period; in the postmenopausal period (age > 45 years with amenorrhea for at least twelve months or any age with amenorrhea for at least six months and a serum level of follicle stimulating hormone (FSH) > 40 IU/l]), be permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy) or have inability to become pregnant for other reasons;
•If you can become pregnant, you need to practice a highly effective contraceptive method compatible with local regulations regarding the use of contraceptive methods for participants participating in clinical studies: e.g., established use of oral hormonal contraception methods, injected or implanted; placement of an intrauterine device or intrauterine system; barrier methods: condom with spermicide in foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical hood) with spermicide in foam/gel/film/cream/suppository; sterilization of the partner (the vasectomized partner should be the only partner for that participant); abstinence (when this is in accordance with the participant's preference and common lifestyle).
Note: if the possibility of becoming pregnant changes after the beginning of the study (e.g., women who are not heterosexually active, pre-menarche women who start to have menarche) the woman should start a highly effective method of contraception, as

described above. It is not recommended to initiate hormonal contraception for the purpose of the study.
A woman who may become pregnant needs to have a negative serum pregnancy test (β-gonadophine human (β HCG]) or a pregnancy test by negative urine at screening.
26) A sexually active man with a woman who may become pregnant and who has not been vasectomized must agree to use a double barrier method of contraception, e.g., condom with foam/gel/film/cream/spermicide suppository or partner with occlusive buffer (diaphragm or cervical cap/vaginal fornice) with foam/gel/film/cream/suppository, and all men also cannot donate sperm during the study, from the moment of the first dose to the last dose of the study drug.
27) Participation in another pharmacotherapeutic or experimental medical device study in the period of thirty days before the beginning of the study treatment.
28) Prescription of daily use of non-steroidal anti-inflammatory agents (INSIs) during initial hospitalization
29) The participant is not willing or unable to make all the visits of the study, as well as the follow-up visit.

4. RANDOMIZATION AND OPEN STUDY

In this study, central randomization will be implemented using the RedCap tool. Participants will be randomly assigned to one of two treatment groups based on a computer-generated randomization schedule prepared prior to the study. Randomization will be balanced using randomly swapped blocks. The study will open label.

5. DOSING AND ADMINISTRATION

The treatment groups in this study are rivaroxaban and standard treatment. Participants will be randomly assigned in a 1:1 ratio to receive 10 mg of rivaroxaban daily or no anticoagulant treatment. The first dose of the study drug should be administered, with medical supervision, no later than one day after the participant leaves the hospital and as soon as possible after randomization. The date and time of the first dose of the study drug and the last dose of LMWH and UFH should be recorded as precisely as possible. All participants should take the study drug daily, with or without food, at approximately the same time each day, and discontinue the study medication after taking the dose on day 35 (see schedule of SCHEDULES AND EVENTS). Regardless of the day on which the visit of day 35±4 occurs, no medication in the study can be taken after day 35. Throughout the study, the study drug will be dispensed at appropriate intervals±
A missed dose should be taken as soon as possible (up to eight hours before the next scheduled dose) and the next scheduled dose should be taken on a regular basis.
In this study, randomization is preceded by hospitalization due to COVID-19 and the phase of treatment with the study drug extends for 35±4 days after randomization, in order to correspond to the period of higher risk of VTE. Chronic therapy with the study drug is not being tested. For these reasons, rivaroxaban will not be provided to the participant after the participant completes the visit of the 60th day.

5.1. Discontinuation of the study medicinal product

The study drug may be temporarily discontinued, if necessary, for invasive procedures or according to medical needs (e.g., at the time of bleeding or prohibited therapy required). If a participant is hospitalized for any reason other than an Event related to VTE or hemorrhage, the study drug should be continued during hospitalization unless the doctor performing the treatment considers that the use of an anticoagulant may

interfere with patient care and may indicate temporary discontinuation or permanent discontinuation of the study drug, provided it is clinically justified. Participants may use an appropriate anticoagulant at the discretion of the doctor who performs the treatment. In this case, the study drug can be restarted upon discharge from the participant and at the discretion of the investigator. These interruptions will be recorded in the RedCap electronic clinical records (eCRF). Intentional discontinuation of the study drug by the participant, unintentional interruption of the study drug, or instructions to temporarily discontinue the study drug by the investigator or other physician will be documented.

6.ADHERENCE TO TREATMENT

The EC will register the study medicine given to the participant. Participants will return the empty vials of the study drug and unused study medicine on the 35±4th visit. The last dose of the study drug should be taken on the 35th, regardless of the day on which the visit takes place on day 35±4.
The accounting of the drug of the study will be carried out at the visit of the 35±4th. Participants should report any unintentional interruption or loss of doses to a research center employee during the visit. It is understood that participants may occasionally forget a dose or that a participant may be placed on temporary discontinuation (see section 5.1, Temporary discontinuation of study treatment).

7.PRE-STUDY AND CONCOMITANT THERAPY

For each participant, the identity of the drug and the dose of the relevant medications used during the initial hospitalization period until the end of the study will be recorded on the appropriate eCRF page: antiplatelet medications (including NATIONS) and anticoagulants, statins and medications relevant to EASs. Only the identity of the drug should be recorded for proton pump inhibitors, glucocorticoids, hormone therapies, including but not, estrogens, progesterone, androgens, antiandrogens and any analogues. If a prohibited medication other than AINEs is received, only the identification of the medication will be recorded.
Prophylactic treatment with LMWH or UFH during initial hospitalization should be reported as precisely as possible in screening.

7.1 Therapy allowed

All decisions regarding concomitant medications are left to the physician who performs the treatment, unless otherwise required by the protocol.

8.STUDY EVALUATIONS

8.1. Study procedures

8.1.1. General aspects

The SCHEDULE OF SCHEDULES AND EVENTS in the synopsis summarizes the frequency and periods of the procedures applicable to this study.
Other serum or urine pregnancy tests may be performed, as determined by the investigator, or as required by local regulations, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.1.2. Screening phase

Screening may begin at any time after admission for initial hospitalization and once free and informed consent has been obtained.
Participants with a modified VTE risk score by the IMPROVE record of 2 or 3 must have a local D dimer value > 2 x LSN prior to randomization to be eligible for the study. For these participants, if d-din was not requested as part of the standard of care by the physician who performs the treatment during initial hospitalization, the center staff may obtain a sample at screening after obtaining free and informed consent. No other screening procedure should be performed until full free and informed consent is obtained. Alternatively, the complete free and informed consent of the study can be obtained if chosen by the study team and necessary to maintain compliance with local requirements and the IRB/Ethics Committee.
Eligibility based on laboratory results will be determined using local laboratory results for laboratory clinical inclusion and exclusion parameters, and the most recent result will also serve as baseline value if there are multiple laboratory values. Laboratory screening assessments that are part of the standard care performed by the investigator do not need to be repeated if performed within the time required by the protocol. A local D-dimer value should be obtained from all participants; if available, a D-dimer value can be used from the screening. If more than one [21] D-dimer value is available, the first value obtained at the beginning of initial hospitalization should be used. The hemoglobin, platelet and serum creatinine count used to determine the CrCl of randomization (calculated using the Cockcroft-Gault formula) needs to be obtained as recently as possible, at least two days before the participant leaves the hospital or later, but before randomization.
Creatinine clearance will be calculated using the Cockcroft-Gault formula, which relates serum creatinine to age (in years) and body weight (in kg) If creatinine concentration is measured in mg/dl, then the following two equations are used for men and women:

men:
$$\frac{[(140 - \text{age [years]}) \text{ weight (kg)}]\times}{[72 \text{ creatinine (mg/dl)}]\times}$$

Women:
$$\frac{[(140 - \text{age [years]}) \text{ weight (kg)}]\times}{[72 \text{ creatinine (mg/dl)}]\times} \times 0{,}85$$

If creatinine concentration is measured in µmol/l, then the following two equations are used for men and women:

men:
$$\frac{[(140 - \text{age [years]}) \text{ weight (kg)}]\times}{[0.814 \text{ creatinine (µmol/l)}]\times}$$

Women:
$$\frac{[(140 - \text{age [years]}) \text{ weight (kg)}]\times}{[0.814 \text{ creatinine (µmol/l)}]\times} \times 0{,}85$$

All screening activities should be completed prior to randomization and results should be available to the investigator for analysis to ensure that eligibility criteria are met.

8.1.3. Open treatment phase

8.1.3.1. Day 1/day of randomization

If the participant meets all inclusion criteria and no exclusion criteria, he/she will be eligible to be randomly randomized to receive rivaroxaban or standard treatment (without anticoagulant treatment) at the day 1 visit.

Randomization should occur on the same day that the participant leaves the hospital, being also allowed the next day after the participant leaves the hospital. Randomization may occur in the hospital, clinic, or other post-discharge destination.

In the randomization visit, before randomization occurs, the center team needs to analyze the schedule of visits and emphasize the importance of completing the study both to the participant and to any family members present. Randomization should not occur if the participant:

- Patient does not agree to return for the face-to-face visit of the day 35±4

•Do not believe that you will have sufficient support to comply with the protocol;

•You are discharged to a destination other than the home and the acceptability of participation in the study has not been confirmed with the accepting physician; or

•If there is planned anticoagulation or post-discharge thromboprophylaxis.

•Participant to present any of the exclusion criteria described in section 3.2.

In addition, before randomization occurs, the center's team should review eligibility criteria, including concomitant medications administered during initial hospitalization and planned on discharge. Special attention should be paid to ensure that acceptable types and doses of thromboprophylaxis were used during initial hospitalization, that no prohibited medications have been administered and that these are not planned.

After randomization, the first dose of the study drug should be administered as soon as possible and no later than the day after hospital discharge. The time of the first dose should be recorded as accurately as possible and should not be delayed depending on the recent administration of LMWH or UFH or to allow supervised administration to occur. The date and time of administration of the first dose of the study drug will be noted in the source documentation and in the eCRF. The participant will be instructed to take the study drug daily until the 35th. Regardless of the day on which the visit of day 35±4 occurs, no medication in the study can be taken after day 35.

In addition, during the randomization visit, the importance of reporting signs and symptoms associated with hemorrhage, DVT and PE will be highlighted.

In the case of bleeding events, participants, and family members, as relevant, will be instructed to:

•Seeking medical attention if bleeding occurs;

•To contact the research center team or the study investigator before the time of the next dose of the study medication; and

•To inform the healthcare professionals in charge of the treatment about participation in the study.

Participants and family members, as relevant, will also be instructed to:

•About the risk of DVT and EP of the participant;

•About the signs and symptoms of VTE and PE;

•Seeking medical attention if any of these signs or symptoms occurs;

•To contact the research center team or the study investigator as soon as symptoms develop and before the time of the next dose of the study medication; and

•To inform the healthcare professionals in charge of the treatment about the participation in the study and the risk of DVT and PE of the participants.

The participant's family must be instructed not to take too long to contact the center and, if necessary, an unscheduled visit may be made.

8.1.3.2. Treatment visits

Participants will be instructed to respect the schedule of visits in the SCHEDULE OF SCHEDULES AND EVENTS. Treatment visits should be made at the center, but to allow the most complete follow-up possible, they can be carried out at home or in another destination of discharge, if allowed by local regulatory requirements and by the IRB/Ethics Committee. The visits of the 7th and the 60th can be made in the form of a telephone visit. Home visits may be performed only by clinically qualified personnel (e.g., training and training) as delegated by the principal investigator and documented in the delegation record. If it is not possible to make a visit with the presence of the participant, one should try telephone contact with him. If it is not possible to make telephone contact with the participant, the center should try to contact other people who are aware of the participant, as permitted by local regulatory requirements and the IRB/Ethics Committee indicating contact with third parties in medical records.

8.1.3.3. Visit of the 7th

The visit of the 7th can be conducted at the clinic or in another destination of discharge including a home visit, if allowed by local requirements, or by telephone visit. Home visits may be carried out only by clinically qualified personnel as delegated by the principal investigator and documented in the delegation registry. Regardless of the form of communication with the participant, this contact must be recorded in a source document. The range of visits is 2 days/+5 days. The study team will confirm sufficient supply of the drug to allow daily dosing until the 35th visit and will strengthen the dosage schedule and the following procedure if a dose is forgotten. The clinical status analysis for suspected outcome events, as well as symptom assessment, consisting of a set of scripted questions, will be completed.

Adverse events and concomitant medications will be collected and described in the eCRF and source document in all contacts with the participant, committing us to present the necessary documentation to the regulatory authorities.

8.1.3.4. Visit of the day 35±4

The visit of the day 35±4 can be conducted in the clinic or in another destination of discharge including a home visit, if allowed by local requirements. Home visits may be performed only by clinically qualified personnel (e.g., training and training) as delegated by the principal investigator and documented in the delegation record. The visit of the day 35±4 should not be conducted as a telephone visit. The visit interval is -0 days/+4 days to ensure that all events until the end of treatment are captured. The last dose of the study drug will be administered on the 35th regardless of the day of the visit of day 35±4, no medicine in the study can be taken after day 35. The drug will be counted in the study and analysis of the clinical status regarding the suspicion of outcome events, as well as the evaluation of symptoms, consisting of a set of scripted questions and a clinical evaluation. Adverse events and concomitant medication will be collected.

On the visit of the 35±4th will be held:

Doppler ultrasound of the lower limbs for detection of asymptomatic VTE according to the protocol used at the institution.

Chest angiography with protocol for PTE and primary pulmonary thrombosis according to the protocol used at the institution.

8.1.3.5. Permanent discontinuation of the study drug/early withdrawal of the study

If the participant permanently discontinues the study medication before day 35±4, he/she should be instructed to make an unscheduled visit and the remaining scheduled visits, including visits from day 7 (-2d/+5 d), day 35 (+4d) and day 60 (±5d) (see SCHEDULE OF SCHEDULES AND EVENTS). Because the primary analysis of the efficacy of the study is based on the principle of intention of treatment (ITT), the researcher should inform the participant about the importance of attending all visits of the study. It is essential for the integrity and results of the clinical study to have verification of vital conditions and other results. If the participant refuses or is unable to attend any visits, the center shall collect as much follow-up information as possible, including contact with the participant or his/her acceptable legal representative by telephone or mail to determine the vital situation and whether a result has occurred as agreed by the participant during the initial process of free and informed consent. If applicable, the vital situation and other results should be obtained by analyzing the participant's clinical or public records, unless this contact is not permitted by local regulations.±
If the participant withdraws his/her consent to the study, this must be recorded in the source document and the participant will be invited to Remain only with telephone contacts in order to ensure the assessment of patient safety and monitoring during the EoT visit.

8.1.4. Post-treatment phase (follow-up)
8.1.4.1. Visit of the day 60

The visit of the 60th day can be conducted in the clinic or in another destination of discharge including a home visit, if allowed by local requirements and by the IRB / Ethics Committee, or by telephone visit. Home visits may be performed only by clinically qualified personnel (e.g., training and training) as delegated by the principal investigator and documented in the delegation record. The range of visits is -5 days/+5 days. The analysis of the clinical status for suspected outcome events, as well as the evaluation of symptoms, will be completed.
If the information is obtained by telephone contact, written documentation of the communication for review in the source documents must be available.
In this study, randomization is preceded by hospitalization due to acute disease and the phase of treatment with the study drug extends for 35±4 days after randomization, in order to correspond to the period of higher risk of VTE. Chronic therapy with the study drug is not being tested. For these reasons, rivaroxaban will not be provided to the participant after the participant completes the visit of the 60h (±5d), unless required by local regulations. The EC will determine whether the population at risk will benefit from the treatment only after the data from the entire study are analyzed.

9.EVALUATIONS AND EFFICACY RESULTS

Since MICHELE is a clinical study guided by symptomatic and asymptomatic events, it is essential that all efficacy outcome events, including symptomatic PE, are properly diagnosed. Any suspicious event that includes symptoms or signs suggestive of VTE should be submitted for evaluation. Researchers are encouraged to carefully consider

the diagnosis of VTE in participants hospitalized under their care with symptoms or exacerbations of conditions such as (pneumonia, bronchitis, heart failure, cardiorespiratory failure, and exacerbation of COPD). Investigators are also firmly encouraged to immediately contact the doctor who performs the treatment in the event of any participant hospitalized with any of these conditions.

9.1. Evaluations and efficacy results

This is a clinical study of results. The primary efficacy result is the composition of all events of symptomatic VTE (DVT of the lower extremities and non-fatal PE) and death related to VTE (death by PE or death in which PE cannot be excluded as the cause) in combination with asymptomatic VTE (detected by Doppler ultrasound of the lower limbs and pulmonary angiography performed after hospital discharge), in addition to acute myocardial infarction, Non-hemorrhagic stroke, major adverse limb event (arterial ischemia) or cardiovascular death in clinically ill patients with COVID-19 at high risk for VTE.
Death will be attributed to one of the following:
CV Death;
Death related to VTE;
Death related to VTE - death due to confirmed PE, documented by objective tests or autopsy;
PE-related death cannot be ruled out – death that cannot be attributed to a documented cause and for which pulmonary embolism cannot be ruled out (unexplained death);
Another CV death; or
Death not CV – death not included in one of the above categories.

Symptomatic DVT – demonstration of signs or symptoms of distal or proximal DVT of the lower extremities, DVT of the upper extremities, or other DVT and confirmed by evaluation, based on one or more of the following diagnostic criteria:
a noncompressible venous segment on compression ultrasound or in patients with previous history of DVT, a new noncompressible venous segment, or a substantial increase (4 mm or more) in vein diameter during total compression in a previously abnormal segment on ultrasound;
The presence of an intraluminal filling defect in venography; or
DVT documented at autopsy.

If in patients with previous history of DVT or if incomplete documentation of a previous episode is available, additional criteria can be integrated to evaluate the current event, such as: thrombus appearance on ultrasound or D-din at presentation. Sole or muscular DVT and superficial VT of the lower extremities will not be included. All available clinical, imaging and laboratory findings should be considered

Symptomatic PE – demonstration of signs or symptoms suggestive of PE and confirmed by evaluation based on one or more of the following diagnostic criteria:
A defect of intraluminal filling in a ct angiography or spiral CT angiography;
A defect of intraluminal filling in a pulmonary angiography or cutting of a vessel with a diameter greater than 2.5 mm; or
A pulmonary perfusion examination of at least 75% of a segment with corresponding normal ventilation (high probability ventilation-perfusion (V-Q) test);

An abnormality on a V-Q exam without high probability associated with DVT documented by ultrasound or venography;
In the absence of an imaging test in a hemodynamically unstable patient, evidence of right ventricular dysfunction by transthoracic or transesophageal echocardiography (Criteria of the European Society of Cardiology [ESC]); or
EP documented at autopsy.

The anatomical extent of THE will be classified by the evaluation committee as segmental or larger, or subsegmental. All clinical and laboratory findings should be considered.

Secondary efficacy results are:

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Symptomatic or fatal VTE
A composition of symptomatic venous thromboembolism and all-cause mortality
A composition of symptomatic venous thromboembolism, myocardial infarction, non-haemorrhagic stroke, and cardiovascular death (death from known cardiovascular disease and death in which the cardiovascular disease cause cannot be excluded).

Any clinical event that suggests the possibility of an efficacy outcome event (including ACS and ITC) should be indicated on the eCRF clinical status page and will be submitted for evaluation. For imaging studies, a copy of the original study with the evaluation package should be sent. For further testing, a report of the results will suffice. All clinical data should be sent to the CPB for evaluation. The ECC may request additional images to ensure appropriate evaluation. The CPB will apply the definitions contained in the CPB chart to assess and classify events, being blind in relation to the designated treatment. The evaluated results will be used for the final analyses.
All evaluations and secondary efficacy results described in Section 9.1 will be evaluated by CPB (defined below).

Myocardial infarction
It requires the combination of evidence of myocardial necrosis (changes in cardiac biomarkers or postmortem pathological findings) and clinical presentation support information, ECG changes, or cardiac imaging results or coronary artery images. All clinical results, ECG and cardiac biomarkers should be considered:
Clinical presentation consistent with the diagnosis of myocardial ischemia and infarction, taking into account differential conditions associated with elevations in cardiac biomarkers;
Elevations of biomarkers;
Elevations related to the upper reference limit (URL) of creatine kinase (creatine kinase, CK), isoenzyme MB of creatine kinase (CK-MB) or troponin;
ECG changes
ECG manifestations of acute myocardial ischemia (in the absence of left ventricular hypertrophy and left branch block); abnormalities may be minor in patients with abnormal biomarkers.;
New elevation of TS at point J in two contiguous variations with the shutdown points: ≥ 0.1 mV in all variations other than V2-V3, where the following shutdown points apply:

≥ 0.2 mV in men aged ≥ 40 years (≥ 0.25 mV in men aged < 40 years) or ≥ 0.15 mV in women;
New depression of the Horizontal ST or with a slope down ≥ 0.05 mV in two contiguous leads and/or new inversion of T ≥ 0.1 mV in two contiguous variations with prominent R wave or proportion of R/S > 1;
Criteria for pathological Q wave
Any Q wave in The V2-V3 leads (abnormalities may be lower in patients with abnormal biomarkers) of 0.02 seconds or QS complex in the V2 and V3 leads;
Wave Q ≥ 0.03 seconds and with depth ≥ 0.1 mV or QS complex n leads I, II, aVL, aVF or V4-V6 in either of the two leads of a contiguous lead grouping (I, aVL, V1-V6, II, III and aVF; the same criteria are used for the V7-V9 supplementary leads and for cabrera's frontal flat derivation grouping);
ECG changes with previous myocardial infarction
Pathological Q waves, as defined above;
In which R ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a positive T wave agreeing in the absence of driving defect;
Criteria for previous myocardial infarction
Pathological Q waves with or without symptoms in the absence of non-ischemic causes;
Imaging evidence of a region of absence of viable myocardium that is thin and cannot contract in the absence of a non-ischemic alteration;
Pathological findings of a anterior myocardial infarction;
5. Stroke – an acute episode of focal or global neurological dysfunction caused by non-traumatic injury to the brain or spinal cord as a result of bleeding or infarction.

9.2. Approach to the participant with efficacy outcome event

If a participant is suspected to have an efficacy outcome event during the study, the physician who performs the treatment should exercise clinical judgment and follow the guidelines established to apply the standard of care. At the discretion of the doctor who performs the treatment, the routine measures described below can be considered:
•Temporarily discontinue treatment with the study medicine as clinically indicated. The disclosure of the study drug should not be necessary, as anticoagulant regimens do not require adjustment, regardless of the assigned treatment group, when administered at the doses used in this study; and
•Perform the necessary diagnostic procedures and consider common treatment measures for VTE and/or cardiac ischemic events if physical examination and diagnostic tests suggest that benefit can be obtained.
After the clinical evaluation of the efficacy outcome event has been completed, the restarting of the study drug may be considered if none of the conditions requiring permanent discontinuation are present (Section 10.2.3, Permanent discontinuation of study treatment) and after consultation with the medical monitor. If the decision is made to restart the study drug (Section 10.2.1, Temporary discontinuation of study treatment), the guidelines for restarting the study drug (Section 10.2.2, Approach to participants with temporary discontinuation of study treatment) may be followed, if applicable, based on the clinical judgment of the investigator.

9.2Safety assessments and results

9.2.1. Hemorrhagic events

The study will include the following safety and tolerability assessments according to the time points demonstrated in the SCHEDULE AND EVENTS: significant hemorrhage, clinically relevant non-ISTH hemorrhage, other bleeding, adverse events, and laboratory clinical trials.
The study will use the ISTH Hemorrhagic Event Classification Scale to assess bleeding events such as significant hemorrhage, clinically relevant non-significant hemorrhage, or other bleeding. Like efficacy results, the same independent CPB will evaluate and classify hemorrhagic events according to the definitions of the CPB chart. The CPB will also classify bleeding events using the *Bleeding Academic Research Consortium scale* as a supportive approach.
The main safety result for this study is major bleeding using the hemorrhage criteria validated according to ISTH. Other safety findings are clinically relevant non-significant hemorrhage and other bleeding. A combination of major, clinically relevant non major and other bleeding is the secondary safety outcome.
A major bleeding event according to ISTH is defined as evident hemorrhage that is associated with:
•A hemoglobin decreases of 2 g/dl or more.
•Transfusion of two or more units of red blood or whole blood concentrates.
•A critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; or
•A fatal result.
Clinically relevant non-significant bleeding is defined as an evident hemorrhage not meeting the criteria of significant bleeding, but associated with medical intervention, unscheduled contact (visit or phone call) with a doctor, interruption (temporary) of study treatment, or associated with discomfort to the participant such as pain or impairment of daily activities.
Examples of clinically relevant non-significant hemorrhage:
•Epothesis if it lasts more than five minutes, if it is repetitive (i.e., two or more episodes of true bleeding, i.e., spots on a handkerchief, within 24 hours), or that leads to an intervention (stating, electrocautery, etc.);
•Gingival bleeding if it occurs spontaneously (i.e., not related to tooth brushing or feeding), or if it lasts longer than five minutes;
•Hematuria, if macroscopic, and spontaneous or last longer than 24 hours after instrumentation (e.g., catheter placement or surgery) of the urogenital tract;
•Macroscopic gastrointestinal hemorrhage: at least one episode of melena or hemathesis, if clinically apparent.
•Rectal blood loss, if more than a few points.
•Hemoptysis, if more than a few stains on the sputism.
•Intramuscular hematoma.
•Subcutaneous hematoma if the size is greater than 25 cm2 or greater than 100 cm2 if caused; and
•Multiple-origin hemorrhage.
Another hemorrhage is defined as any other episode of evident bleeding that does not meet the ISTH criteria for significant or non-significant clinically relevant hemorrhage.
In the eCRF, details of all bleeding events will be recorded.
All suspected bleeding events will be sent for evaluation.

9.2.2. Approach to the participant with a bleeding event

If a participant has a bleeding event during treatment with the study medicine, the following routine measures should be considered:
•Delay the next administration of the study medicine or discontinue treatment if indicated. Rivaroxaban has a plasma half-life of approximately 5 to 9 hours and, in some participants, up to thirteen hours. Therefore, temporary discontinuation of the study drug may allow the control of hemorrhage. Disclosure of the study drug should not be necessary. As there is no specific reversal agent for rivaroxaban, the treatment of the participant should not be influenced by the knowledge of the drug of the treatment study;
•Consider common treatment measures for bleeding events, including fluid replacement and hemodynamic support, frozen blood, and fresh plasma transfusion, if physical examination and laboratory tests suggest that benefit can be obtained; and
•Consider that all causes other than antithrombotic medication may contribute to the seriousness of the hemorrhagic event (i.e., rule out disseminated intravascular coagulation, thrombocytopenia and other coagulopathies, liver and kidney dysfunction, concomitant medications, etc.) and treat appropriately.
If bleeding cannot be controlled by these measures, consider the administration of one of the following procoagulants (according to the dosages advised in their respective leaflets). [43]
•Activated prothrombin complex concentrate.
•Prothrombin complex concentrate; and
•Recombinant Factor VIIa (NovoSeven®).
All products administered to control bleeding should be inserted into the eCRF.
Note: protamine sulfate and vitamin K are not expected to affect rivaroxaban anticoagulant activity. Currently, there is no scientific justification for the benefit, nor experience with systemic hemostatic (e.g., desmopressin, aprotinin and epsilon-aminocaproic acid).
After resolving the hemorrhagic event, the restart of the study drug can be considered based on the clinical judgment of the investigator.

9.2.3. Other safety assessments

9.2.3.1. Adverse events

Adverse events will be reported by the participant (or, where appropriate, by a caregiver, surrogate, or legally accepted representative of the participant) throughout the duration of the study. Adverse events will be monitored by the investigator as specified in Section 12, Adverse Event Report.

9.2.3.1.1 Clinical laboratory tests

Additional laboratory screening tests by the investigator should not be performed, as these are likely to be part of the participant's hospital evaluation. No pre-specified laboratory tests will be performed during the study. However, these participants are likely to perform local laboratory tests during their initial hospitalization period. Any laboratory test, along with reference intervals relevant to a serious adverse event or outcome event, should be recorded on the appropriate eCRF page.
The following test results with reference intervals will be obtained from the laboratory of the local hospital/laboratory during the initial hospitalization period:
Hematology;
Hemoglobin;

Platelet count;
Serum creatinine (CrCl to be calculated by RedCap using Cockcroft-Gault formula;
D-dimer; and
Test for pregnancy or urine only for women who may become pregnant.

9.3. Risk-benefit ratio

The risk-benefit ratio of rivaroxaban will be explored by the analysis of combined efficacy and safety events, using number need to treat and number needed to harm.

9.4. Collection and handling of samples

The exact dates and times of sample collection must be recorded in the eCRF or laboratory requisition form. If blood samples are collected through a catheter, an appropriate amount (1 ml) of fluid slightly larger than the volume of the dead space of the lock will be removed from the catheter and discarded before each blood sample is collected. After blood sample collection, the catheter should be handled according to local practices.

10.Completion/Withdrawal of The Participant

10.1. Conclusion

The total duration for a participant who completes the study after randomization is expected to be 60 days.
All possible efforts and measures will be made to collect the complete vital conditions and other data resulting from randomization until the visit of day 60 (±5d) for each randomized participant in this study, regardless of compliance with the study medication or visits. In the case of participants with loss of follow-up or who have withdrawn consent from the study, efforts will be made to obtain their vital conditions and other results from permitted sources.
In cases where participants indicate that they do not want to "continue", researchers should determine whether this refers to discontinuation of the treatment of the study (the most expected scenario), unwillingness to attend follow-up visits, unwillingness to have telephone contact, unwillingness to have any contact with the study team, or unwillingness to allow contact with a third party (e.g., family member, doctor). In all cases, every effort should be made to continue to monitor the participant, and vital conditions and other outcomes should be determined for all randomized participants.

10.2. Discontinuation of study treatment

If a treatment of the participant's study must be discontinued before the end of the double-blind treatment phase, the participant should continue to be monitored for efficacy and safety outcomes.
During the study, if the participant develops any clinical picture that, at the discretion of the investigator, requires anticoagulant thromboprophylaxis or long-term fibrinolysis, the treatment of the study will be temporarily discontinued or permanently discontinued for the participant and the participant will be treated as considered appropriate by the doctor who performs the treatment. The participant will be asked to continue the study so that he/she can be monitored for efficacy and safety results.

10.2.1. Temporary discontinuation of study treatment

If the participant needs re-hospitalization (re-hospitalization is defined as a total combination of hospitalization and/or stay in the ER ≥ 24 hours) during treatment with the study drug for reasons other than primary efficacy or bleeding results, the participant should continue to receive the study drug at the investigator's discretion. If the doctor who performs the treatment considers that the participant needs any anticoagulant during re-hospitalization, the study drug should be temporarily discontinued and may be resumed after hospital discharge. Mechanical methods of prophylaxis may be used during hospitalization. If this method is chosen, the study medicine may be maintained. In addition, the study drug should be temporarily discontinued if the participant:
•Develop any clinical picture that may require the use of anticoagulant therapy, thromboprophylaxis, fibrinolysis or that presents an increased risk of bleeding;
•Undergo percutaneous coronary intervention, coronary artery revascularization, any other intervention procedure that may require the use of anticoagulant therapy, thromboprophylaxis, or that presents an increased risk of bleeding. For temporary discontinuation of the study drug for an elective procedure or surgery, it is suggested that the researchers follow the guidelines contained in the package leaflet of the drug.
•Present important bleeding event other than intracranial hemorrhage (in the case of less severe bleeding events, the investigator's criterion is allowed; if possible, the study medicine should be resumed when the bleeding event is resolved, and the cause has been identified and corrected);
•If the participant develops a new neurological deficiency or significant change in mental conditions suggesting a stroke. As soon as the diagnosis is definitively made and the appropriate treatment is provided, the study drug may be restarted at the discretion of the investigator;
•Develop a platelet count of less than 50,000/µl. If a repeated platelet count is obtained and the result indicates that the abnormal platelet count was false, the study drug may be restarted. If the finding was not false, the study drug may be restarted after two consecutive values greater than 75,000/µl, with an interval of at least one week, have been obtained;
•Present a serious adverse event that is considered by the investigator to be possibly related to, or exacerbated by, the administration of the study drug; or
•Need a therapy prohibited on a temporary basis (see Section 7, Pre-study, and concomitant therapy).

10.2.2. Approach to participants with temporary discontinuation of study treatment

If the study medicinal product is temporarily discontinued to allow a procedure to be carried out, the routine measures described should be considered.

10.2.3. Permanent discontinuation of study treatment

If a participant needs to be permanently discontinued from the study drug before the end of the double-blind treatment phase, this will not result in automatic withdrawal of the study participant, and the participant should continue to be followed up for efficacy and safety results.
The participant should be permanently discontinued from the study medicinal product if:

•The investigator believes that for safety reasons (i.e. adverse events) it is in the participant's best interest to discontinue the study drug;
•The participant develops any clinical picture requiring anticoagulant or thromboprophylaxis that extends beyond the treatment phase of the study (e.g., atrial fibrillation, VTE);
•The participant become pregnant;
•The participant has a creatinine clearance drop below 20 ml/min or two consecutive measurements below 30 ml/min with an interval of at least one week (calculated by the Cockcroft-Gault formula, see Section 8.1.2) during the study;
•The participant needs hemofiltration or dialysis on a permanent basis;
•The participant requests to discontinue the study drug permanently; or
•The participant has a hemorrhagic stroke or intracranial hemorrhage.
If the participant permanently discontinues the study drug before the 35th, he/she should be instructed to make an unscheduled visit and the remaining scheduled visits, including visits from day 7 and day 21 (if they have not yet been completed) and visits of day 35±4 and day 60 (±5d). The visit of the day 35 should be a visit to the clinic; the visit of the 60th can be carried out by phone.
The eCRF should be completed to identify the reason for permanent discontinuation of the study drug. The researcher will provide a narrative to describe any adverse events that occur until the visit of the 60th (±5d). Appropriate sections of adverse event or serious adverse event of eCRF should be completed. If the study drug is terminated due to a serious adverse event, the issuance of an immediate report (within 24 hours) is also necessary, as described in Section 12.3.2, Serious adverse events.

10.3. Withdrawal from study

A participant will be removed from the study for any of the following reasons:
•Loss of follow-up (only after all means of all subsequent contacts, including location services, when permitted by law, until the visit of the 60th (± 5d), have been exhausted, the loss of follow-up will be declared); or
•Withdrawal of consent (unless specifically refused by the participant, the participant will be contacted to obtain the vital situation and other results on the visit of the 60th (±5d).
In the event of loss of follow-up of a participant, every possible effort should be made by the study center staff to contact the participant and determine the reason for discontinuation/withdrawal. The follow-up measures should be documented.
The study drug allocated to one retired participant cannot be allocated to another participant. Participants who withdraw from the study will not be replaced.
If the participant withdraws the consent of the study or there is loss of follow-up, his vital situation and other results will be collected on the visit of the 60th (±5d) by telephone or in person, or if necessary, by an analysis of the participant's medical or public records, unless this contact is not permitted by local regulations.

11.STATISTICAL METHODS

Statistical analysis will be done independently by researchers.
An overview of the statistical methods to be used to analyze the efficacy and safety of the study drug is outlined below. A more detailed SAP, including detailed rules for missing or partially missing data, will be provided in a separate document that will be finalized before the first participant is randomized.

Abstracts will be provided per treatment group using descriptive statistics appropriate for all study variables including demographic and baseline characteristics. No imputation will apply unless otherwise specified in SAP. Descriptive statistics, such as mean, median, standard deviation, minimum and maximum, will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables.
Unless otherwise indicated, all statistical tests will be interpreted at a nominal significance level (i.e. without multiplicity adjustments) of 0.05 and all ICs at a two-tailed nominal level of 95%.
The results analyzed on efficacy and safety results will be used for partial and final analyses.

11.1. Analysis set and analysis phase

Each analysis involves the following two aspects: 1) set of analysis, specifying the participants to be included; and 2) analysis phase, specifying the period in which the data will be included. The main analysis sets and analysis phases are defined below.

11.1.1. Analysis sets

•Intention of treatment (ITT) (as set out in the E9 guideline of the International Harmonization Conference [ICH]): this set of analysis consists of all randomized participants who have a signed and valid free and informed consent form;
•According to protocol (PP): This set of analysis is a subset of the ITT analysis set. Participants with significant protocol deviations will be excluded from the PP analysis set. Significant protocol deviations will be defined in SAP; and
•Safety: This set of analysis is a subset of the ITT analysis set, which consists of participants who received at least one dose of the study drug.

11.1.2. Analysis phases

•Until day 35±4: this analysis phase includes all randomization data up to day 35±4 (inclusive)
•On treatment: this phase of analysis includes all data between randomization and two days after the last dose of the study drug (inclusive).

11.2. Sample size determination

With the incidence of about 50% of thromboembolic phenomena in patients hospitalized with COVID-19 and estimating a relative risk reduction (RRR) of 66.67% based on the findings of the MARINER study (which included only symptomatic events) in the primary efficacy outcome based on the ITT analysis set and analysis phase up to day 35±4 (RRR is defined as 1 minus the [HR] risk ratio of rivaroxaban versus standard treatment);
Statistical power of 80% assuming the RRR above; and
The two-tailed significance level is 0.05.
Dropout rate of 10%
It is estimated that, in total, approximately 320 participants are randomized for rivaroxaban or standard treatment in a ratio of 1:1. This estimate is based on an

estimated incidence rate for standard treatment of the primary efficacy outcome of 15% in the control group and 5% in the active group.

11.3. Efficacy analyses

11.3.1. Primary efficacy outcome

The primary efficacy outcome is a combination of symptomatic VTE (DVT and non-fatal PE) and VTE-related death (death by EP or death in which cannot be excluded as the cause) in combination with VTE detected by Doppler ultrasound and/or chest angiotomography performed on day 35±4 post-discharge in addition to MI, non-hemorrhagic stroke, MALE and CV death. In the ITT analysis set and analysis phase until day 35±4.
Using the ITT population, the **relative risk (RR)** or **risk ratio** is the ratio of the probability of an outcome in an exposed group (treatment) to the probability of an outcome in an unexposed group (control). Relative risk measures the association between the exposure and the outcome.

All patients in the treatment group are compared with all patients in the control group. The efficacy analysis tests will be one-sided, with a type I error rate of 2.5%, assuming a two-sided 95% confidence interval. The cumulative incidence of the composite of events will be compared between the rivaroxaban and control group, and the **relative risk (RR)** or **risk ratio** will be estimated.
The superiority of the treatment is claimed if the upper limit of 95% confidence interval is less than one.
Primary outcome results will be presented according to Table 2.
For the safety analysis, statistical tests will be two-sided, with a type I error rate of 5% and a two-sided 95% confidence interval.

11.3.2 Secondary efficacy analysis

Secondary efficacy outcome are:
•VTE-related death (death by PE or death in which PE cannot be excluded as the cause) and symptomatic VTE (DVT of the lower extremities and non-fatal PE);
•The composition of symptomatic VTE (DVT of the lower extremities and non-fatal PE) and all-cause mortality;
•The composition of symptomatic VTE (DVT of the lower extremities and non-fatal PE), myocardial infarction (IM), non-hemorrhagic stroke and cardiovascular death (CV) (death from known CV and death in which the CV cause cannot be excluded; by this definition, a VTE-related death is considered a CV death).

Relative risks will be reported with the respective 95% confidence intervals for binary outcomes. For continuous outcomes, mean differences between the groups will be reported with the respective 95% confidence intervals. It is intended to present the secondary and safety outcomes as described in detail on the SAP.

Exploratory efficacy results

Each exploratory result will be summarized by treatment groups based on the ITT analysis set and the analysis phase up to day 35±4.

11.4 Safety analysis

11.4.1. Primary safety outcomes

The primary safety outcome is major bleeding according to ISTH criteria.
This result will be analyzed based on ITT analysis, and the relative risks will be reported with the respective 95% confidence intervals for binary outcomes. For continuous outcomes, mean differences between the groups will be reported with the respective 95% confidence intervals. It is intended to present the secondary and safety outcomes as described in detail on the SAP.

11.4.2 Secondary safety outcomes

The secondary safety outcomes are a combination of major, clinically relevant non-major and other bleeding, as well as subcategories of significant bleeding, including critical sites, will also be summarized by treatment groups. This result will be analyzed based on ITT analysis, and the relative risks will be reported with the respective 95% confidence intervals for binary outcomes. For continuous outcomes, mean differences between the groups will be reported with the respective 95% confidence intervals. It is intended to present the secondary and safety outcomes as described in detail on the SAP.

Sensitivity Analyses

We planned sensitivity analyses with the same principles described for the primary outcome in the ITT population using the Per Protocol population.

11.4.4 Adverse events

For adverse events that are collected as specified in section 12, ADVERSE EVENT REPORT, the preferred terms reported in the eCRF by researchers to identify adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). For each term preferred by MedDRA, the percentage of participants who present at least one occurrence of a certain event will be summarized by treatment group. Additional summaries, listings or participant narratives may be provided as appropriate.

11.4.5 Clinical laboratory tests
Because this study does not collect laboratory data regularly, laboratory data will not be summarized. Local laboratory data can be discussed in the participant's narratives.

12.REPORT OF ADVERSE EVENTS

Timely, accurate and complete reporting and analysis of safety information from clinical studies are critical to the protection of participants, researchers, and the EC, and are required by regulatory agencies around the world. The EC has established standard operating procedures in compliance with regulatory requirements worldwide to ensure proper communication of safety information. All clinical studies conducted by the EC, or its affiliates will be conducted in accordance with these procedures.
Rivaroxaban has been widely studied in phase 1 to phase 4 clinical studies involving more than 70,000 patients and its overall adverse event profile has been well described. Appropriate information regarding adverse events was systematically collected and submitted to regulatory authorities. All safety data and results will be reviewed regularly by a non-blind IMCD.
Section 12.1.1 describes the common definitions of adverse events and serious adverse events.

12.1. Settings

12.1.1. Definitions and classifications of adverse events

12.1.1.1 Adverse event

An adverse event is any undesirable medical occurrence in a clinical study participant who receives a drug product (under investigation or not). An adverse event does not necessarily have a causal relationship with treatment. An adverse event may therefore be any sign (including an abnormal laboratory finding), unfavorable and unintentional disease or symptom, temporally associated with the use of a medicinal product (under investigation or not), whether related to the medicinal product (under investigation or not) in question (Definition according to ICH).
This includes any occurrence that is of new onset or with worsening of severity or frequency with respect to baseline condition or abnormal results of diagnostic procedures, including abnormalities of laboratory tests.
Note: the EC collects adverse events from the signature of the ICF (see Section 12.3.1, All adverse events, in relation to the period of the last adverse event record).

12.1.1.2 Serious adverse event

A serious adverse event based on ich and EU guidelines for pharmacovigilance of medical products for human use is any undesirable medical occurrence that at any dose:
•Results in death.
•Be life-threatening
(Participant presented a risk of death at the time of the event. It does not refer to an event that, hypothetically, could have caused death if it were more serious.);
•Requires hospitalization or prolongation of a pre-existing hospitalization.
•Results in persistent or significant disability/disability.
•Be a congenital anomaly/defect.
•Be a suspected transmission of any infectious agent by means of a medicinal product; or
•Be clinically important.
Note: medical or scientific judgment should be exercised to decide whether it would be appropriate to report other situations such as important medical events that may not be

life-threatening immediately, or result in death or hospitalization, but which may put the participant at risk or require intervention to avoid one of the other results indicated in the definition above. These should also be considered serious.
For the purposes of this study, efficacy and safety results will not be considered as adverse events or serious adverse events.

12.1.1.3 Unlisted (unexpected) adverse event/reference safety information

An adverse event is considered unlisted if the nature or severity is not consistent with the relevant product safety information applicable. For rivaroxaban, the anticipation of an adverse event will be determined by the presence or absence of the term listed in the researcher's brochure[19].

12.1.1.4 Adverse event associated with the use of the drug

An adverse event is considered associated with the use of the drug if the assignment is possible, probable, or very likely, according to the definitions indicated in section 12.1.1.

12.2 Timelines and reporting processes

All adverse events and special reporting situations, whether serious or not serious, will be reported from the moment any signed and dated ICF is obtained until the completion of the last procedure related to the participant's study (which may include contact for security monitoring). Serious adverse events, including those spontaneously reported to the investigator until day 60 (± 5d) visit, should be reported using the serious adverse event form. The EC shall assess any safety information that is reported spontaneously by an investigator after the period specified in the protocol.
All adverse events, regardless of seriousness, severity, or purported relation to the study medication, should be recorded using medical terminology in the source document. Whenever possible, diagnosis should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). The researchers should record their opinion regarding the relationship of the adverse event to the therapy of the study, in addition to setting the date of start and end of that reported by the participant. All measures necessary for the treatment of the adverse event should be recorded in the source document and reported in accordance with the EC instructions.
The EC assumes responsibility for the proper reporting of adverse events to regulatory authorities. The EC will also notify the researcher (and the head of the research institute, if required) of any suspected unexpected serious adverse reactions (SUSARs). The appropriate investigator (or EC, when required) must report SUSARs to the appropriate Independent Ethics Committee/Research Ethics Committee (IEC/IRB) that approved the protocol, unless documented and otherwise required by the IEC/IRB. A SUSAR will be notified in a non-blind manner to regulatory authorities. Participating investigators and IEC/IRB will receive a summary of SUSAR on a blind side, unless otherwise specified.
The EC assumes responsibility for the proper reporting of adverse events to regulatory authorities. The EC will also report to the investigator (and the head of the investigational institute when necessary) all serious adverse events that are not listed (unexpected) and associated with the use of the study drug. The appropriate investigator (or EC, when required) must report these events to the appropriate Independent Ethics

Committee/Research Ethics Committee (IEC/IRB) that has approved the protocol, unless documented and otherwise required by the IEC/IRB.

12.3. Reporting serious adverse events

All serious adverse events that occur during the study should be reported to the appropriate EC contact person by the research team within 24 hours of taking note of the event.
Information about serious adverse events will be transmitted to the EC using the serious adverse event form, which must be completed and signed by a study center physician and sent to the EC within 24 hours. Initial and follow-up reports of a serious adverse event should be made by e-mail regulatorio@svriglobal.com.
All serious adverse events that have not been resolved by the end of the study or that have not been resolved by discontinuing the participant's participation in the study should be followed up until any of the following options occur:
•The event resolves itself;
•The event stabilizes;
•The event returns to baseline levels if a baseline value/situation is available;
•The event can be attributed to agents other than the study drug or to factors not related to the study; or
•If it becomes unlikely that any other information can be obtained (refusal of the participant or health professional to provide other information, loss of follow-up after demonstration of due diligence with follow-up efforts).
Any event requiring hospitalization (or extension of hospitalization) that occurs during the participation of a participant in a clinical study should be reported as a serious adverse event, except hospitalizations for the following:
•Social reasons in the absence of an adverse event; and
•Surgery or procedures planned prior to entry into the study (must be documented in the eCRF).

12.4. Pregnancy

All initial pregnancy reports should be reported to the EC by the study centre team within 24 hours of taking note of the event through the appropriate pregnancy notification form. Abnormal pregnancy outcomes (e.g., miscarriage, stillbirth, and congenital anomaly) are considered serious adverse events and should be reported using the serious adverse event form. Any participant who becomes pregnant during the study must discontinue the continuation of the study treatment.
As the effect of the drug under study is unknown in sperm, the pregnancies of partners of participants included in the study will be reported by the study center team within 24 hours of knowing the event through the proper pregnancy notification form.
Follow-up information on the outcome of pregnancy and any postpartum sequelae in the newborn will be required.

12.5.How to contact the EC regarding safety

The names (and respective telephone numbers) of individuals who should be contacted about safety issues or questions about the study are indicated on the contact information page(s).

13.INFORMATION ON THE MEDICINE OF THE STUDY

13.1. Physical description of the study's medicinal product(s)

The study drug provided for this study consists of 10 mg rivaroxaban and corresponding standard treatment. All study medications will be provided as round white tablets. Consult the researcher's brochure for a list of excipients[19].

13.2. Packaging

The study medicine will be supplied in vials and dispensed in child-proof packaging.

13.3. Labelling

The study's drug labels will contain information that meets applicable regulatory requirements.

13.4. Preparation, handling and storage

The storage recommendation for rivaroxaban is at room temperature (approximately 15°C to 30°C).

13.5. Drug accounting

The investigator and/or study team duly delegated by him/her will be responsible for ensuring that all the study medication received at the center is inventoried and accounted for during the study. The dispensing of the study medicinal product to the participant and the return of the study medicinal product by the participant (if applicable) should be documented in the accounting form of the medicinal product. Participants should be instructed to return all original vials, empty or containing the study drug.
The study drug has to be handled in full compliance with the protocol and container label and should be stored in the study center in a limited access area or in a locker with padlock under appropriate environmental conditions. Unused study drugs should be available for verification by the EC study center monitor during monitoring visits to the center. The return to the EC of the unused study medicinal product will be documented in the return form of the medicinal product. When the study center is an authorized destruction unit and supplies of the study medicine are destroyed in the centre, this should also be documented in the drug return form.
The study drug should be distributed under the supervision of the investigator, or a qualified member of the study center staff, or by a hospital pharmacist/clinic. The study drug will only be provided to study participants. The returned study drug should not be distributed again, even if it is to the same participant. The study drug cannot be relabeled or redistributed for use by other participants. The investigator agrees not to distribute the study drug, nor store it in any centre other than the study centers agreed with the EC.

14.STUDY SPECIFIC MATERIALS

The researcher will receive the following supplies:
•Researcher brochure;

•Pharmacist's manual/product manual under investigation of the study center;
•Manual of electronic data capture (RedCap).

15.ETHICAL ASPECTS

15.1. Study-specific design considerations

Potential participants will be properly informed about the risks and requirements of the study, and, during the study, participants will receive new information that could affect the decision to continue participation. They will be informed that their consent to participate in the study is voluntary and can be withdrawn at any time, without explanation and without any penalty or loss of benefits to which they would be entitled. Only participants who are fully able to understand the risks, benefits and potential adverse events of the study and provide their consent voluntarily will be included.
This study was designed to closely simulate the current clinical practice of discontinuation of anticoagulants at hospital discharge. More than 90% of hospital post-discharge patients do not continue thromboprophylaxis with anticoagulants. In addition, thromboprophylaxis treatment is limited by an increasing trend of lower hospital admissions. Since VTE events still occur after hospital discharge, there is a need to assess the current standard of care. A comparator standard treatment group is therefore justified to evaluate this paradigm of post-hospital discharge treatment. The risk of bleeding will be reduced in this clinically ill high-risk population by adjusting the dose and excluding subgroups of patients with a comparatively high risk of bleeding, e.g. active cancer.
Any participant with a clinical picture requiring the use of any parenteral or oral anticoagulant (e.g., atrial fibrillation) during the study is not eligible for participation. During the study, if the participant develops any clinical picture that, at the discretion of the investigator, requires anticoagulant, fibrinolysis or thromboprophylaxis, the treatment of the study will be discontinued for the participant and the participant will be treated as considered appropriate by the doctor who performs the treatment. The participant will be asked to continue the study so that he/she can be monitored for efficacy and safety results.
Rivaroxaban has been studied in more than 70,000 patients for the treatment or prevention of associated thrombotic diseases. Because the safety profile of rivaroxaban and the risk of hemorrhage with its use are well known, blood collections were kept to a minimum in this fragile group of participants. Participants will be submitted to all other treatments and diagnostic tests according to the standard of care in their locality, causing this study to interfere minimally in their regular health care routine.
Researchers should inform the participant of the importance of completing all study visits if their study drug is discontinued early due to an adverse event or other reasons to assess the vital situation and determine whether outcome events may have occurred. If participants refuse visits in the office, the investigator should remind the participant about the importance of allowing regular contact until the end of the study, according to the SCHEDULE OF SCHEDULES AND EVENTS, occurring with them or with a legally accepted representative, a close friend or family member, or his family doctor to determine the vital situation and whether efficacy and safety results occurred.

15.2. Regulatory ethical compliance

15.2.1. Investigator responsibilities

The investigator is responsible for ensuring that the clinical study is conducted in accordance with the protocol, ich's current guidelines on good clinical practice (BPC) and applicable and country-specific regulatory requirements.
Good clinical practices are an international ethical and scientific quality standard for planning, conducting, recording and reporting studies involving the participation of human beings. Compliance with this standard provides a public guarantee that the rights, safety and well-being of study participants are protected, in line with the principles of the Helsinki Declaration, and that the study data are credible.

15.2.2. Independent Ethics Committee or Research Ethics Committee

Prior to the start of the study, the investigator (or EC, where required) will provide the IEC/IRB with up-to-date and complete copies of the following documents (as required by local regulations):
•Final protocol and, if applicable, amendments;
•EC-approved ICF (and any other written material to be delivered to participants);
•Researcher brochure (or equivalent information) and amendments/addends;
•Recruitment materials for ec approved participants;
•Compensation information in case of study-related injuries or payment to participants for participation in the study, if applicable;
•Researcher curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB);
•Information regarding funding, EC name, institutional affiliations, other potential conflicts of interest and incentives for participants; and
•Any other document that IEC/IRB requests to fulfill its obligation.
This study will be carried out only after the IEC/IRB has granted full approval of the final protocol, amendments (if any, excluding those that are purely administrative, without any consequence for the participants, data or conduct of the study), ICF, applicable recruitment materials, compensation programs to the participant, and the EC having received a copy of this approval. This letter of approval must be dated and clearly identify the IEC/IRB and the documents being approved.
During the study, the researcher (or the EC, where required) will send the following documents and updates to the IEC/IRB for review and approval, where appropriate:
•Amendments to the protocol (excluding those that are purely administrative, without consequences for the participants, data or conduct of the study);
•Review(s) of the ICF and any other written material to be delivered to participants;
•If applicable, new or revised participant recruitment materials approved by the EC;
•Reviews of compensation in case of study-related injuries or payment to participants for participation in the study, if applicable;
•New edition(s) of the researcher's brochure and amendments/addends
•Summaries of the study situation at intervals stipulated in the IEC/IRB guidelines (at least annually);
•Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug;
•New information that may adversely affect the safety of participants or the conduct of the study;
•Deviations or changes to the protocol to eliminate immediate risks to participants;
•Report of deaths of participants under the care of the investigator;
•Notification if a new investigator becomes responsible for the study at the centre;
•Development security update report and linear listings, if applicable; and

•Any other IEC/IRB requirement.
For all amendments to the protocol (excluding those that are purely administrative, without consequences for the participants, data or conduct of the study), the amendment and revisions applicable to the ICF must be promptly submitted to the IEC/IRB for analysis and approval prior to the implementation of the amendment(s).
At least once a year, IEC/IRB will be asked to review and re-approve this clinical study. The new approval must be documented in writing (excluding those that are purely administrative, with no consequences for participants, data or conduct of the study).
At the end of the study, the investigator (or the EC, when required) will notify the IEC/IRB of the end of the study.

15.2.3. Free and informed consent form

Each participant must provide written consent in accordance with local requirements after the nature of the study has been fully explained. Exceptionally due to the contagious nature and according to the recommendations of regulatory agencies, during hospitalization participants will give their consent through electronic ICF with the help of eCRF. Invariably, during the return consultations of days 7 or 35, participants must manually sign the Informed Consent in two ways in physical format, initialing all pages with the researcher who will make the consultation. One copy will be delivered to the participant while the other will be archived in the research center. The ICF(s) must be signed/s, in this case electronically, before performing any activity related to the study. The ICF(s) used must be approved by both the EC and the IEC/IRB and must be in a language that the participant can read and understand. The free and informed consent form must comply with the principles that originated in the Helsinki Declaration, current ICH and BPC guidelines, applicable regulatory requirements, and EC policy. Prior to inclusion in the study, the investigator or an authorized member of the study center team should explain to potential participants the objectives, methods, reasonably expected benefits, and potential risks of the study, and any discomfort that participation in the study may entail. Participants will be informed that participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the medical care that participants will receive for the treatment of the disease. Participants will be informed that alternative treatments are available if they refuse to participate, and that such refusal will not harm future treatment. Finally, you will be informed that the investigator will keep a participant identification record for long-term follow-up purposes, if necessary, and that their records can be accessed by the EC's authorized health authorities and staff, without violating the participant's confidentiality, to the extent permitted by applicable law(s) or regulations. By signing the ICF, the participant is authorizing such access, including the permission to obtain information about their survival conditions and agrees to allow their study physician to contact the participant again to obtain consent for other safety assessments, if necessary, and subsequent treatments related to the disease, or to obtain information about their survival condition.
If the participant refuses or is unable to return for the visit of the 35th (± 4d) and/or follow-up visit of the 60th (± 5d), the center must collect as much information as possible, including contact with the participant or his legally accepted representative by telephone or mail to determine the vital situation and whether a resulting event occurred, as agreed by the participant during the initial process of free and informed consent.

The participant will have enough time to read the ETS, and opportunity to ask questions. After this explanation, and before the entry into the study, the consent must be duly registered after dated and digitally signed in the inclusion of the study and personally during the follow-up visit by the participant. After obtaining consent, a copy of the ICF must be given to the participant.
If the participant is unable to read or write, an impartial witness must be present throughout the process of free and informed consent (which includes reading and explaining all written information) and must date and personally sign the ICF after the participant's verbal consent.

15.2.4. Confidentiality of personal data

The collection and processing of personal data of the participants enrolled in this study will be limited to the data necessary to meet the objectives of the study.
This data should be collected and processed with appropriate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures may be taken to protect personal data against unauthorized disclosure or access, accidental or criminal destruction, or accidental loss or alteration. The EC team whose responsibilities require access to personal data agrees to keep the identity of the study participants confidential.
The ICF obtained from the participant includes explicit consent for the processing of personal data and for the researcher/institution to allow direct access to their original medical records (data/source documents), for monitoring related to the study, auditing, analysis by the IEC/IRB and regulatory inspection. This consent also includes the transfer of data to other entities and other countries.
The participant has the right to request, through the researcher, access to his/her personal data and the right to request rectification of any data that is not correct or complete. Sensible steps will be taken to respond to such requests, taking into account the nature of the request, the conditions of the study and the applicable laws and regulations.

16.ADMINISTRATIVE REQUIREMENTS

16.1. Amendments to protocol

Neither the investigator nor the EC will modify this protocol without a formal amendment by the EC. All amendments to the protocol must be issued by the EC and dated and signed by the investigator. Amendments to the protocol may not be applied without prior approval by the IEC/IRB, or where the relevant competent authority finds reasons for non-acceptance, except where necessary to eliminate immediate risks to participants, at which time the amendment shall be immediately submitted to the IEC/IRB and the relevant competent authority. The documentation approving the amendment by the researcher and the IEC/IRB must be provided to the EC. When the change(s) involve so only logistical or administrative aspects of the study, the IRB (and the IEC, when required) will only need to be notified.
During the study, in situations where a deviation from the protocol is unavoidable, the investigator or other doctor on duty will contact the appropriate EC representative (see the contact information page(s) provided separately). Except in emergencies, this contact must be made before applying any deviation from the protocol. In all cases, contact with the EC should be made as soon as possible to discuss the situation and agree on an appropriate procedure for action. The data recorded in the eCRF and source

documents will reflect any deviation from the protocol, and the source documents will describe such deviation and the circumstances that require it.

16.2. Regulatory documentation

16.2.1. Regulatory approval/notification

This protocol and any amendment to it shall be submitted to the regulatory authorities of the respective country, if applicable. A study cannot be started until all local regulatory requirements are met.

16.2.2. Documentation required for pre-study

The following documents must be provided to the EC prior to sending the study medicinal product to the study centre:
•Protocol and amendment(s), if applicable, signed and dated by the principal investigator;
•A copy of the written, dated and signed (or sealed, if applicable, in accordance with local regulations) approval of the Protocol IEC/IRB, amendments, ICF, any recruitment material and, where applicable, compensation programs to participants. This approval shall clearly identify the specific protocol by title and number, and shall be signed (or sealed, if applicable by local regulations) by the director or authorized representative;
•IEC/IRB name and address, including a current list of IEC/IRB members and their positions, with a statement that it is organized and operates in accordance with bpc and applicable laws and regulations. If accompanied by a letter of explanation or equivalent from the IEC/IRB, a general statement may replace that list. If a researcher or a member of the investigation team is a member of the IEC/IRB, documentation should be obtained stating that this person did not participate in the deliberations or the vote/opinion on the study;
•Approval or notification of regulatory authorities, if applicable;
•Signed and dated statement from the investigator (e.g., FDA Form 1572), if applicable;
•Documentation of the qualifications of researchers (e.g., curriculum vitae);
•Financial disclosure form of the researcher completed by the principal investigator, whenever necessary;
•Contract of the signed and dated clinical study, which includes the financial agreement; and
•Any other documentation required by local regulations.

The following documents must be provided to the EC prior to the inclusion of the first participant:
•Financial disclosure forms of the researcher completed by all sub-investigators;
•Documentation of the qualifications of sub-researchers (e.g., curriculum vitae);
•Name and address of any local laboratory conducting tests for the study and a dated copy of the current normal laboratory ranges for such tests, if applicable; and
•Local laboratory documentation demonstrating competence and reliability of the tests (e.g. accreditation/certificate), if applicable.

16.3. Records of identification, inclusion and screening of participants

The researcher undertakes to fill out a registration of identification and inclusion of participants to allow easy identification of each participant during and after the study. The completeness of this document will be analyzed by the EC contact at the study center.
The registration of identification and inclusion of participants will be treated as confidential and will be filed by the investigator in the study file. To ensure the confidentiality of the participant, no copies will be made. All reports and communications related to the study will identify participants by identifying and deing date of birth of the participant. In cases where the participant is not randomized to the study, the date on which he/she was seen and the date of birth will be used.
The investigator also needs to complete a participant screening record that informs all participants who were interviewed to determine eligibility for inclusion in the study.

16.4. Source documentation

In order to confirm the data collected in the eCRF, the source documentation should be available at least for the following: participant identification, eligibility and study identification; discussion of the study and date of signature of the free and informed consent form; dates of consultations; results of safety and efficacy parameters as required by the Protocol; record of all adverse events and follow-up of adverse events; concomitant medications; records of receipt/distribution/return of the drug; information on the administration of the study medicinal product; and date of completion of the study and reason for early discontinuation of the study drug or withdrawal from the study, if applicable.
In addition, the author of a data insertion in the source documents must be identifiable. At a minimum, the type and level of detail of the source data available to a study participant should be compatible with those typically recorded at the study center as a basis for standard medical care. The specific details required as source data for the study will be analyzed together with the investigator prior to the study and will be described in the monitoring guidelines (or another equivalent document).

16.5. Filling out the clinical form

Clinical records will be provided to the researchers before the visits in printed or electronic format referring to each participant.
Electronic data capture (RedCap) will be used for this study. The study data will be transcribed by the study team of the source documents for an eCRF and transmitted securely to the EC within the period agreed between the EC and the study center. The electronic file will be considered to be the CRF.
Spreadsheets will be used to capture some data in order to facilitate the completion of the CRF. Any of these worksheets will become part of the attendee's source documentation. All data related to the study should be recorded in the eCRFs prepared by the EC. The data must be entered in the eCRF. The designated study center team should complete the eCRF as soon as possible after a visit from the participant, and the forms should be available for analysis on the next scheduled monitoring visit.
The investigator must confirm that all data records in the eCRF are accurate and correct. All records, corrections and changes in eCRF must be made by the investigator or other authorized team of the study center. If necessary, questions ("*queries*") will be raised in

the RedCap tool. The investigator or an authorized member of the study center team should adjust the CRF (if applicable) and respond to the question.
The investigator or a study center team member should adjust the CRF (if applicable) and answer the question.
If CRF corrections are required after initial registration in CRF, this can be done in three different ways:
•The study center team can make corrections to the RedCap tool on their own initiative or in response to an automatic question (generated by the Rap tool);
•The manager of the study center can generate a question for solution by the research team; or
•The clinical data manager can generate a question for solution by the investigation team.

16.6. Quality assurance/data quality control

Measures to be taken to ensure the accuracy and reliability of the data include the selection of qualified investigators and appropriate research centers, analysis of protocol procedures with the investigator and associated team prior to the study, and periodic monitoring visits from the EC, and direct transmission of laboratory clinical data from a central laboratory to the EC representative database. Written instructions will be given for the collection, preparation, storage and sending of samples.
The EC will analyze the eCRF for accuracy and completeness during monitoring visits at the study center and after transmission to the EC; any discrepancies will be resolved with the investigator or representative as appropriate. After loading the data into the clinical study database, it will be checked for accuracy and consistency with the data sources.

16.7. Record retention

In accordance with ICH BPC guidelines, the researcher/institution will keep all CRFs and all source documents that support the data collected from each participant, as well as all study documents as specified in Section 8 of BPC/ICH, Essential Documents for conducting a clinical study, and all study documents as specified by applicable regulatory requirements. The investigator/institution shall take measures to prevent the accidental or premature destruction of such documents.
All essential documents must be retained by the researcher for at least two years after the last approval of a marketing application in an ICH region and until there is no pending or contemplated application for marketing in an ICH region, or that at least two years have passed since the formal discontinuation of the clinical development of the product under investigation. These documents shall be retained for a longer period if required by due regulatory requirements or by an agreement with the sponsor (SVRI). It is the sponsor's responsibility to inform the investigator/institution when these documents no longer need to be kept.
If the investigator responsible retires, changes, or for other reasons is exempt from the responsibility of keeping the study records, custody should be transferred to a person who accepts responsibility. The EC shall be notified in writing of the name and address of the new person in charge. Under no circumstances shall the investigator transfer or discard any study documents before obtaining written approval from the EC.

If it is necessary for the EC or the appropriate regulatory authority to examine any documentation relating to this study, the researcher/institution shall allow access to such information.

16.8. Monitoring

The EC will carry out monitoring visits to the centre as often as necessary. The monitor will post the dates of the visits in a visit log of the study center, which will be kept in the center. In these visits, the monitor will compare the data entered in the CRF with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all original data sources required to complete the CRF are known to the EC and study center staff, and to be accessible for verification by ec contact at the study center. If electronic records are kept in the study center, the verification method should be discussed with the investigation team.
Remote data monitoring will be performed by the study monitor. The participant's key demographic data, study center performance data, and other key variable data will be monitored remotely as part of regular monthly data monitoring for all centers and compared to results generally seen for that country and region. Centers identified as having participants with data that are substantially out of normal may also be subject to face-to-face monitoring visits.
Direct access to source documentation (medical records) should be allowed for the purpose of verifying whether the data recorded in the CRF are consistent with the original source data. The findings of this analysis of the eCRFs and source documents will be discussed with the investigation team. The EC expects that during monitoring visits, the relevant study center staff will be available, the source documentation will be accessible and an appropriate environment for analyzing study-related documents is provided. The monitor will meet with the investigator on a regular basis during the study to provide information about the conduct of the study.
In addition to monitoring visits in the center, remote contacts may occur. During these remote contacts, the study team is expected to be available to provide an update on the progress of the study at the center.

16.9. Conclusion/closing of the study

16.9.1. Conclusion of the study

The study is considered completed after the last evaluation of the last participant of the study. The final data of the study center will be sent to the EC (or representative) after the completion of the final evaluation of the participant in that centre, within the period specified in the clinical study contract.

16.9.2. Closure of the study

The EC reserves the right to close the study centre or close the study at any time, for any reason, at the EC's discretion. The study centers will be closed upon completion of the study. A study center is considered closed when all necessary documents and study supplies have been collected and a center closing visit has been performed.
The researcher may initiate the closure of the study centre at any time, provided there are reasonable grounds, and a notification is given with sufficient time before the planned closure.

The reasons for the premature closure of an EC research centre or researcher may include, but is not least:
•Failure of the researcher to adhere to the protocol, the requirements of the IEC/IRB or local health authorities, the EC procedures or the BPC guidelines;
•Inadequate recruitment of participants by the researcher; and
•Discontinuation of the development of the study medicine.

16.10. Centre audits

Representatives of the EC's clinical quality assurance department may visit the center at any time during or after the study is completed to conduct an audit of the study in accordance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with CRF. The participant's privacy, however, must be respected. The researcher and his team are responsible for being present and available for consultation during routine audit visits scheduled to the study center, carried out by the EC or its representatives. Similar audit procedures may also be conducted by agents of any regulatory body as part of a national BPC compliance program or to analyze the results of this study to support a regulatory submission. The investigator must immediately notify the EC if contacted by a regulatory agency regarding a nearby inspection.

16.11. Use of information and publications

All information, including but not including, but not only, information with respect to rivaroxaban or EC operations (e.g., patent application, formulas, manufacturing processes, basic scientific data, previous clinical data, formulation information) provided by the EC to the researcher and not previously published, and any data, including exploratory research data, generated as a result of this study, is considered confidential and remains the sole property of the EC. The investigator agrees to keep this information confidential and use it only to conduct this study, and not to use it for other purposes without the prior written consent of the EC.
The researcher understands that the information developed in the clinical study will be used by the EC in connection with the continued development of rivaroxaban, and thus may be disclosed as necessary to other clinical investigators or regulatory agencies. In order to enable information from clinical studies to be used, the researcher is obliged to make available to the EC all the data obtained in the study.
The results of the study will be reported in a clinical study report generated by the EC, and this will contain CRF data from all research centers that participated in the study, laboratory clinical data from a central laboratory in the EC representative database. Recruitment performance or specific knowledge related to the nature and key evaluation parameters of the study will be used to define a coordinating investigator. The results of exploratory analyses performed after csr has been published may be reported in a separate report and will not require revision of the CSR. The identification elements of the search participant will not be used in the publication of results. Any work created in the course of the execution of the study and contained in the data that may benefit from the protection of copyright (except any publication by the investigator, as provided below) will be the property of the EC, as author and owner of the copyright of that work.
In line with good publication practices and the guidelines of the International *Publication Practices and International Committee of Medical Journal Editors,* the EC

shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The researcher has the right to publish the specific data of the study center after the primary data are published. If a researcher wishes to publish study information, a copy of the manuscript shall be provided to the EC for review at least sixty days prior to submission for publication or presentation. Immediate analysis will be organized for abstracts, poster presentations or other materials. If requested by the EC in writing, the investigator shall retain that publication for up to another sixty days to allow the submission of a patent application. In the event of questions arising regarding scientific integrity or regulatory compliance, the EC will examine these issues with the researcher. The EC will not dictate changes in scientific content and has no right to delete information. For multicenter study plans and sub-study approaches, secondary outcomes should generally not be published before the main outcomes of a study have been published. Similarly, researchers will recognize the integrity of a multicenter study by not submitting for publication data from each study center until the combined results of the completed study have been submitted for publication within twelve months of the availability of final data (tables, listings, graphs), or until the EC confirms that there will be no publication of the multicenter study. The authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the uniform requirements for manuscripts sent to biomedical journals, which state that the nominated authors should have made a significant contribution to the study plan or analysis and interpretation of the data, made the critical analysis of the work and given the final approval of the final version.

16.11.1. Record of clinical studies and dissemination of results

The EC will record and/or disclose the existence of the results of clinical studies as required by law.

17. References - protocol

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